(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 April 2004 (22.04.2004)

PCT

(10) International Publication Number
WO 2004/032827 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US2003/015856

(22) International Filing Date: 20 May 2003 (20.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/382,156 20 May 2002 (20.05.2002) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; P. O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RIPKA, Amy** [US/US]; 63A Elm Street, Branford, CT 06405 (US). **CAMPBELL, Jeffrey, Allen** [US/US]; 525 Alpine Drive, Cheshire, CT 06410 (US). **GOOD, Andrew, Charles** [US/US]; 52 High Hill Road, Wallingford, CT 06492 (US). **SCOLA, Paul, Michael** [US/US]; 107 Georgetown Drive, Glastonbury, CT 06033 (US). **SIN, Ny** [US/US]; 6 Curry Lane, East Hampton, CT 06424 (US). **VENABLES, Brian** [US/US]; 27 Mattabesset Drive, Durham, CT 06422 (US).

(74) Agents: **VOLLES, Warren, K.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/032827 A2

(54) **Title:** HEPATITIS C VIRUS INHIBITORS

(57) **Abstract:** The present invention relates to tripeptide compounds, compositions and methods for the treatment of hepatitis C virus (HCV) infection. In particular, the present invention provides novel tripeptide analogs, pharmaceutical compositions containing such analogs and methods for using these analogs in the treatment of HCV infection.

HEPATITIS C VIRUS INHIBITORS

FIELD OF THE INVENTION

The present invention is generally directed to antiviral compounds, and more specifically directed to compounds which inhibit the functioning of the NS3 protease encoded by Hepatitis C virus (HCV), compositions comprising such compounds and methods for inhibiting the functioning of the NS3 protease.

BACKGROUND OF THE INVENTION

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma. (Lauer, G. M.; Walker, B. D. *N. Engl. J. Med.* (2001), 345, 41-52).

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. (Poynard, T. et al. *Lancet* (1998), 352, 1426-1432). Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy (Zeuzem, S. et al. *N. Engl. J. Med.* (2000), 343, 1666-1672). However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive

stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

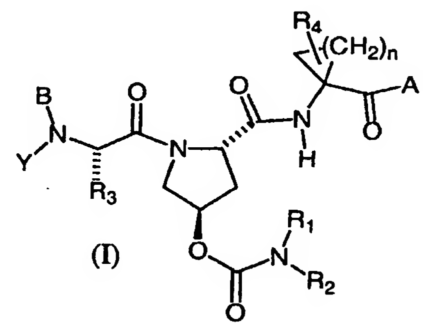
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. At least six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the possible effect of genotypes on pathogenesis and therapy.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non- structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one, as yet poorly characterized, cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the N-terminal region of NS3 (henceforth referred to as NS3 protease) and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A- NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a cofactor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A seems necessary to the processing events, enhancing the proteolytic efficiency at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

Among the compounds that have demonstrated efficacy in inhibiting HCV replication, as selective HCV serine protease inhibitors, are the peptide compounds disclosed in U.S. Patent No. 6,323,180.

SUMMARY OF THE INVENTION

The present invention provides compounds including pharmaceutically acceptable salts, solvates or prodrugs thereof, having the structure of Formula I wherein:



(I)

(a) R_1 is: H, C_{1-6} alkyl, C_{2-10} alkenyl or C_{6-10} aryl, all of which may be substituted with halo, cyano, nitro, C_{1-6} alkoxy, amido, amino or phenyl;

R_2 is:

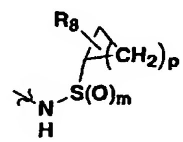
(i) C_{1-6} alkyl; C_{1-6} alkyl substituted with a carboxy (C_{1-6} alkyl); C_{3-7} cycloalkyl; C_{3-6} cycloalkyl (C_{6-10} aryl); C_{2-10} alkenyl; C_{1-3} alkyl (C_{6-10} aryl); all of which may be substituted from one to three times with halo, C_{1-3} alkyl or C_{1-3} alkoxy; or R^2 is C_{5-9} heterocycle, which may be substituted from one to three times with halo, C_{1-4} alkyl, (C_{1-6} alkyl) carboxy or phenyl; or

(ii) C_{6-10} aryl, which may be substituted from one to three times with the following: halo; C_{1-6} alkyl which itself may be substituted with one to three halo; C_{1-6} alkoxy; nitro; thio (C_{1-6} alkyl); phenyl; C_{1-6} alkanoyl; benzoyl; benzoyl oxime; carboxy; carboxy (C_{1-6} alkyl); (C_{1-6} alkyl) carboxy; phenoxy; (C_{1-6} alkyl) carboxy (C_{1-6} alkyl); or C_{6-10} aryl which may be substituted with a C_{5-9} heterocycle, which heterocycle includes one to three nitrogen, oxygen or sulfur atoms and

which heterocycle itself may be substituted with C_{1-3} alkyl, C_{1-3} alkoxy, $-CF_3$ or (C_{1-3} alkyl) carboxy; or

(b) R_1 and R_2 may join to form a 5 or 6 membered heterocycle, or join to form a 5 or 6 membered heterocycle fused with one or two C_6 aryl groups;

(c) A is -OH, C_{1-6} alkoxy, $-N(H)SO_mR^5$



where p is 1, 2 or 3, and R_8 is trialkylsilane; halo; C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-\overset{O}{\overset{\|}{C}}-R_9$ wherein R_9 is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-\overset{O}{\overset{\|}{C}}-OR_{10}$ wherein R_{10} isC_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-\overset{O}{\overset{\|}{C}}-NR_{11}R_{12}$, wherein R_{11} and R_{12} are each independentlyC_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy;

C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-SO_2R_{13}$ wherein R_{13} is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

or $-\mathrm{O}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}R_{14}$ wherein R_{14} is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

(d) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl, each optionally substituted from one to three times with halogen; or R_2 is H; or R_2 together with the carbon to which it is attached forms a 3, 4 or 5 membered ring;

(e) R_5 is C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; C_{1-8} alkyl; unsubstituted C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl); or unsubstituted or substituted Het, said Het substituents being the same or different and being selected from one to three of halo, cyano, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, amido, C_{1-6} alkanoylamino, amino, phenyl or phenylthio, said phenyl or phenyl portion of phenylthio being unsubstituted or substituted by one to three, same or different, substituents selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, amido or phenyl

(f) m is 1 or 2;

(g) n is 1 or 2;

(h) R_3 is C_{1-8} alkyl optionally substituted with halo, cyano, amino, C_{1-6} dialkylamino, C_{6-10} aryl, C_{7-14} alkylaryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, wherein the cycloalkyl or alkylcycloalkyl are optionally substituted with hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} alkoxy; or R_3 together with the carbon atom to which it is attached forms a C_{3-7} cycloalkyl group optionally substituted with C_{2-6} alkenyl;

(i) Y is H, phenyl substituted with nitro, pyridyl substituted with nitro, or C_{1-6} alkyl optionally substituted with cyano, OH or C_{3-7} cycloalkyl; provided that if R_4 or R_5 is H then Yis H;

(j) B is H, C_{1-6} alkyl, R_6-(C=O)-, R_6O(C=O)-, R_6-N(R_7)-C(=O)-, R_6-N(R_7)-C(=S)-, R_6SO_2-, or R_6-N(R_7)-SO_2-;

(k) R_6 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, -OC(O)C_{1-6} alkyl, C_{1-6} alkoxy, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalklyl, each optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (iii) C_{6-10} aryl or C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl, halogen, nitro, hydroxy, amido, (lower alkyl) amido, or amino optionally substituted with C_{1-6} alkyl; (iv) Het; (v) bicyclo(1.1.1)pentane; or (vi) -C(O)OC_{1-6} alkyl, C_{2-6}alkenyl or C_{2-6} alkynyl; and.

(l) R_7 is H; C_{1-6}alkyl optionally substituted with 1-3 halogens; or C_{1-6} alkoxy provided R_6 is C_{1-10} alkyl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

The present invention also provides compositions comprising the compounds or pharmaceutically acceptable salts, solvates or prodrugs thereof and a pharmaceutically acceptable carrier. In particular, the present invention provides pharmaceutical compositions useful for inhibiting HCV NS3 comprising a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable carrier.

The present invention further provides methods for treating patients infected with HCV, comprising administering to the patient a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof. Additionally, the present invention provides methods of inhibiting HCV NS3 protease by administering to a patient an effective amount of a compound of the present invention.

By virute of the present invention, it is now possible to provide improved drugs comprising the compounds of the invention which can be effective in the treatment of patients infected with HCV. Specifically, the present invention provides peptide compounds that can inhibit the functioning of the NS3 protease, e.g., in combination with the NS4A protease.

DETAILED DESCRIPTION OF THE INVENTION

Stereochemical definitions and conventions used herein generally follow McGraw-Hill Dictionary of Chemical Terms, S. P. Parker, Ed., McGraw-Hill Book Company, New York (1984) and Stereochemistry of Organic Compounds, Eliel, E. and Wilen, S., John Wiley & Sons, Inc., New York (1994). Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory and (+) or d, meaning the compound, is

dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer of a mirror image pair may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture.

The nomenclature used to describe organic radicals, e.g., hydrocarbons and substituted hydrocarbons, generally follows standard nomenclature known in the art, unless otherwise specifically defined. Combinations of groups, e.g., alkylalkoxyamine, include all possible stable configurations, unless otherwise specifically stated. Certain radicals and combinations are defined below for purposes of illustration.

The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical composition, but differ with regard to the arrangement of the atoms or groups in space.

The term "diastereomer" refers to a stereoisomer which is not an enantiomer, e.g., a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

The term "enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term "pharmaceutically acceptable salt" is intended to include nontoxic salts synthesized from a compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445. The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

The term "therapeutically effective amount" means the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

The term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of Formula I, and pharmaceutically acceptable salts, and solvates, e.g. hydrates. Similarly, reference to intermediates, is meant to embrace their salts, and solvates, where the context so permits. References to the compound of the invention also include the preferred compounds of Formula II and III.

The term "derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This

physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include hydrates, ethanolates, methanolates, and the like.

The term "prodrug" as used herein means derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become, by solvolysis or under physiological conditions, the compounds of the invention which are pharmaceutically active in vivo. A prodrug of a compound may be formed in a conventional manner with a functional group of the compounds such as with an amino, hydroxy or carboxy group when present. The prodrug derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine.

The term "patient" includes both human and other mammals.

The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutical carrier, i.e., adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Ingredients listed in Remington's Pharmaceutical Sciences, 18^{th} ed., Mack Publishing Company, Easton, PA (1999) for example, may be used.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the

scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable risk/benefit ratio.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

The term “substituted” as used herein includes substitution at from one to the maximum number of possible binding sites on the core, e.g., organic radical, to which the subsitutent is bonded, e.g., mono-, di-, tri- or tetra- substituted, unless otherwise specifically stated.

The term "halo" as used herein means a halogen substituent selected from bromo, chloro, fluoro or iodo. The term “haloalkyl” means an alkyl group that in substituted with one or more halo substituents.

The term "alkyl" as used herein means acyclic, straight or branched chain alkyl substituents and includes, for example, methyl, ethyl, propyl, butyl, tert-butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methypropyl, 1,1-dimethylethyl. Thus, C_{1-6} alkyl refers to an alkyl group having from one to six carbon atoms. The term “lower alkyl” means an alkyl group having from one to six, preferably from one to four carbon atoms. The term “alkylester” means an alkyl group additionally containing on ester group. Generally, a stated carbon number range, e.g., C_{2-6} alkylester, includes all of the carbon atoms in the radical.

The term “alkenyl” as used herein means an alkyl radical containing at least one double bond, e.g., ethenyl (vinyl) and alkyl.

The term "alkoxy" as used herein means an alkyl group with the indicated number of carbon atoms attached to an oxygen atom. Alkoxy includes, for example,

methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is referred to in the art as tert-butoxy. The term "alkoxycarbonyl" means an alkoxy group additionally containing a carbonyl group.

The term "haloalkoxy" as used herein means the radical –O(haloalkyl) wherein haloalkyl is as defined above.

The term "alkanoyl" as used herein means straight or branched 1-oxoalkyl radicals containing the indicated number of carbon atoms and includes, for example, formyl, acetyl, 1-oxopropyl (propionyl), 2-methyl-1-oxopropyl, 1-oxohexyl and the like.

The term "cycloalkyl" as used herein means a cycloalkyl substituent containing the indicated number of carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and spiro cyclic groups such as spirocyclopropyl as spirocyclobutyl. The term "cycloalkoxy" as used herein means a cycloalkyl group linked to an oxygen atom, such as, for example, cyclobutyloxy or cyclopropyloxy. The term "alkylcycloalkyl" means a cycloalkyl group linked to an alkyl group. The stated carbon number range includes the total number of carbons in the radical, unless otherwise specfically stated. This a C_{4-10} alkylcycloalkyl may contain from 1-7 carbon atoms in the alkyl group and from 3-9 carbon atoms in the ring, e.g., cyclopropylmethyl or cyclohexylethyl.

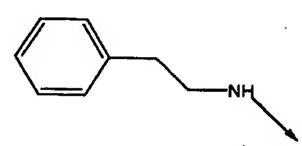
The term "aryl" as used herein means an aromatic moiety containing the indicated number of carbon atoms, such as, but not limited to phenyl, indanyl or naphthyl. For example, C_{6-10} aryl refers to an aromatic moiety having from six to ten carbon atoms which may be in the form of a monocyclic or bicyclic structure. The term "haloaryl" as used herein refers to an aryl mono, di or tri substituted with one or more halogen atoms. The terms "alkylaryl", "arylalkyl" and "aralalkyl" mean an aryl group substituted with one or more alkyl groups. Thus, a C_{7-14} alkylaryl group many have from 1-8 carbon atoms in the alkyl group for a monocyclic aromatic and from 1-4 carbon atoms in the alkyl group for a fused aromatic. The aryl radicals include those substituted with typical substituents known to those skilled in the art, e.g., halo, hydroxy, carboxy, carbonyl, nitro, sulfo, amino, cyano, dialkylamino haloalkyl, CF_3,

haloalkoxy, thioalkyl, alkanoyl, SH, alkylamino, alkylamide, dialkylamide, carboxyester, alkylsulfone, alkylsulfonamide and alkyl(alkoxy)amine. Examples of alkylaryl groups include benzyl, butylphenyl and 1-naphthylmethyl. The terms “alkylaryloxy” and “alkylarylester” mean alkylaryl groups containing an oxygen atom and ester group, respectively.

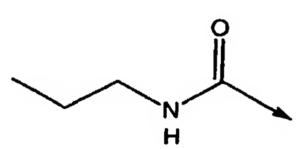
The term "carboxyalkyl" as used herein means a carboxyl group (COOH) linked through an alkyl group as defined above and includes, for example, butyric acid.

The term "alkanoyl" as used herein means straight or branched 1-oxoalkyl radicals containing the indicated number of carbon atoms and includes, for example, formyl, acetyl, 1-oxopropyl (propionyl), 2-methyl-1-oxopropyl, 1-oxohexyl and the like.

The term "amino aralkyl" as used herein means an amino group substituted with an aralkyl group, such as the following amino aralkyl

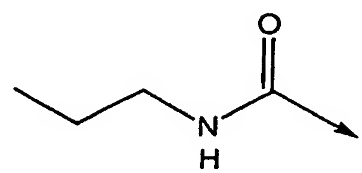


The term "alkylamide" as used herein means an amide mono-substituted with an alkyl, such as



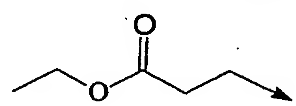
The term "carboxyalkyl" as used herein means a carboxyl group (COOH) linked through a alkyl group as defined above and includes, for example, butyric acid.

The term "alkylamide" as used herein means an amide mono-substituted with an alkyl, such as



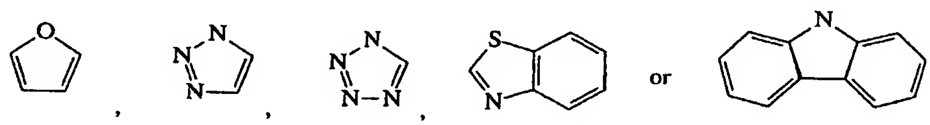
The term "carboxyalkyl" as used herein means a carboxyl group (COOH) linked through an alkyl group as defined above and includes, for example, butyric acid.

The term “alkylcarboxyalkyl” as used herein refers to radicals such as

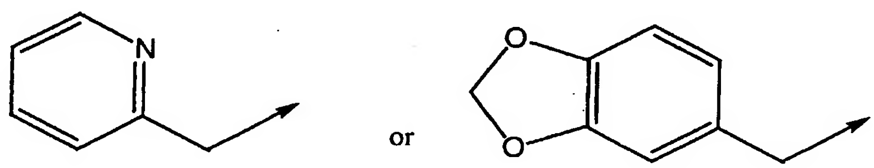


The terms "heterocycle", or “Het” as used herein means a monovalent radical derived by removal of a hydrogen from a five-, six-, or seven-membered saturated or unsaturated (including aromatic) heterocycle containing from one to four heteroatoms selected from nitrogen, oxygen and sulfur. The heterocycles of the present invention include those substituted with typical substituents known to those skilled in the art on any of the ring carbon atoms, e.g., one to three substituents. Examples of such substituents include C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{3-7} cycloalkoxy, halo-C_{1-6} alkyl, CF_3, mono-or di- halo-C_{1-6} alkoxy, cyano, halo, thioalkyl, hydroxy, alkanoyl, NO_2, SH, , amino, C_{1-6} alkylamino, di (C_1-$_6$) alkylamino, di (C_1-$_6$) alkylamide, carboxyl, (C_1-$_6$) carboxyester, C_{1-6} alkylsulfone, C_{1-6} alkylsulfonamide, C_{1-6} alkylsulfoxide, di (C_1-$_6$) alkyl(alkoxy)amine, C_{6-10} aryl, C_{7-14} alkylaryl, and a 5-7 membered monocyclic heterocycle. Furthermore, the term heterocycle includes heterocycles, as defined above, that are fused to one or more other ring structure. Examples of suitable heterocycles include, but are not limited to, pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, thiophene, diazepine, 1H-imidazole, oxazole , pyrazine, isoxazole, thiazole, tetrazole, piperidine, 1,4-dioxane, 4-morpholine,

pyridine, pyrimidine, thiazolo[4,5-b]-pyridine, quinoline, or indole, or the following heterocycles:

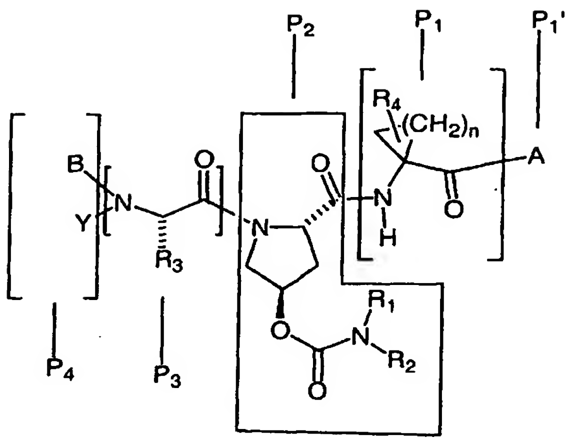


The term "alkyl-heterocycle" as used herein, means a heterocyclic radical as defined above linked through a chain or branched alkyl group, wherein alkyl as defined above containing the indicated number of carbon atoms. Examples of C_{1-6} alkyl-Het include:

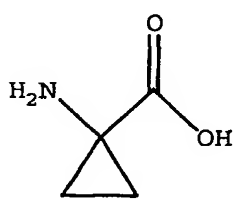


Where used in naming compounds of the present invention, the designations "P1', P1, P2, P3 and P4", as used herein, map the relative positions of the amino acid residues of a protease inhibitor binding relative to the binding of the natural peptide cleavage substrate. Cleavage occurs in the natural substrate between P1 and P1' where the nonprime positions designate amino acids starting from the C-terminus end of the peptide natural cleavage site extending towards the N-terminus; whereas, the prime positions emanate from the N-terminus end of the cleavage site designation and extend towards the C-terminus. For example, P1' refers to the first position away from the right hand end of the C-terminus of the cleavage site (ie. N-terminus first position); whereas P1 starts the numbering from the left hand side of the C-terminus cleavage site, P2 is the second position from the C-terminus, etc.)(see Berger A. & Schechter I., Transactions of the Royal Society London Series (1970), B257, 249-264).

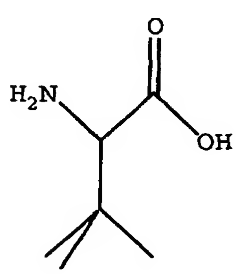
Thus in the compounds of formula I, the "P1' to P4" portions of the molecule are indicated below:



As used herein the term "1-aminocyclopropyl-carboxylic acid" (Acca) refers to a compound of formula:



As used herein the term "*tert*-butylglycine" refers to a compound of the formula:



The term "residue" with reference to an amino acid or amino acid derivative means a radical derived from the corresponding α-amino acid by eliminating the hydroxyl of the carboxy group and one hydrogen of the α-amino acid group. For

instance, the terms Gln, Ala, Gly, Ile, Arg, Asp, Phe, Ser, Leu, Cys, Asn, Sar and Tyr represent the "residues" of *L*-glutamine, *L*-alanine, glycine, *L*-isoleucine, *L*-arginine, *L*-aspartic acid, *L*-phenylalanine, *L*-serine, *L*-leucine, *L*-cysteine, *L*-asparagine, sarcosine and *L*-tyrosine, respectively.

The term "side chain" with reference to an amino acid or amino acid residue means a group attached to the α-carbon atom of the α-amino acid. For example, the R-group side chain for glycine is hydrogen, for alanine it is methyl, and for valine it is isopropyl. For the specific R-groups or side chains of the α-amino acids reference is made to A.L. Lehninger's text on Biochemistry (see chapter 4).

In accordance with the present invention, R_1 may be H, C_{1-6} alkyl, C_{2-10} alkenyl or C_{6-10} aryl, all of which may be substituted with halo, cyano, nitro, C_{1-6} alkoxy, amido, amino or phenyl. Preferably, R_1 is H, C_{1-6} alkyl, C_{2-4} alkenyl or phenyl.

In accordance with the present invention, R_2 may be:

(i) C_{1-6} alkyl; C_{1-6} alkyl substituted with a carboxy (C_{1-6} alkyl); C_{3-7} cycloalkyl; C_{3-6} cycloalkyl (C_{6-10} aryl); C_{2-10} alkenyl; C_{1-3} alkyl (C_{6-10} aryl); all of which may be substituted from one to three times with halo, C_{1-3} alkyl or C_{1-3} alkoxy; or R^2 is C_{5-9} heterocycle, which may be substituted from one to three times with halo, C_{1-4} alkyl, (C_{1-6} alkyl) carboxy or phenyl; or

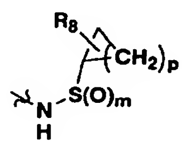
(ii) C_{6-10} aryl, which may be substituted from one to three times with the following: halo; C_{1-6} alkyl which itself may be substituted with one to three halo; C_{1-6} alkoxy; nitro; thio (C_{1-6} alkyl); phenyl; C_{1-6} alkanoyl; benzoyl; benzoyl oxime; carboxy; carboxy (C_{1-6} alkyl); (C_{1-6} alkyl) carboxy; phenoxy; (C_{1-6} alkyl) carboxy (C_{1-6} alkyl); or C_{6-10} aryl which may be substituted with a C_{5-9} heterocycle, which heterocycle includes one to three nitrogen, oxygen or sulfur atoms and which heterocycle itself may be substituted with C_{1-3} alkyl, C_{1-3} alkoxy, $-CF_3$ or (C_{1-3} alkyl) carboxy.

Preferably, R_2 is phenyl, optionally substituted with C_{1-3} alkyl, one to three chloro or one to three fluoro; or R^2 is phenyl, optionally substituted with phenyl,

methoxy, phenoxy, C_{2-4} alkylester, C_{2-6} alkanoyl, nitro, thio (C_{1-4} alkyl) or carboxy. More preferably, R_2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, all of which may be optionally substituted with a phenyl group. Even more preferably, R_2 is a six membered heterocyclic group, optionally substituted with one to three chloro or one to three fluoro, or substituted with a (C_{1-6} alkyl) carboxy. Most preferably, R_2 is C_{2-4} alkenyl

R_1 and R_2 may join to form a 5 or 6 membered heterocycle, or join to form a 5 or 6 membered heterocycle fused with one or two C_6 aryl groups; Preferably, R_1 and R_2 form a five or six membered heterocyclic ring, optionally containing oxygen.

In one aspect of the present invention, A may be –OH, C1-6 alkoxy, -$N(H)SO_mR^5$, or



where p is 1, 2 or 3, and R_8 is trialkylsilane; halo; C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het.

In another aspect of the present invention, A may be $-\overset{\overset{O}{\|}}{C}-R_9$ wherein R_9 is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het.

In another aspect of the present invention, A may be $-\overset{\overset{O}{\|}}{C}-OR_{10}$ wherein R_{10} isC_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14}

alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het.

In another aspect of the present invention, A may be $-\overset{\displaystyle O}{\overset{\|}{C}}-NR_{11}R_{12}$, wherein R_{11} and R_{12} are each independentlyC_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het.

In another aspect of the present invention, A may be $-SO_2R_{13}$ wherein R_{13} is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het.

In another aspect of the present invention, A may be $-O\overset{\displaystyle O}{\overset{\|}{C}}R_{14}$ wherein R_{14} is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het.

In accordance with the present invention, R_3 may be C_{1-8} alkyl optionally substituted with halo, cyano, amino, C_{1-6} dialkylamino, C_{6-10} aryl, C_{7-14} alkylaryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, wherein the cycloalkyl or alkylcycloalkyl are optionally substituted with hydroxy, C_{1-6} alkyl, C_{2-6}

alkenyl or C_{1-6} alkoxy; or R_3 together with the carbon atom to which it is attached forms a C_{3-7} cycloalkyl group optionally substituted with C_{2-6} alkenyl. Preferably, R_3 is C_{1-8} alkyl optionally substituted with C_6aryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl. More preferably, R_3 is C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy; or C_{3-7} cycloalkyl. Most preferably, R_3 is t-butyl

In accordance with the present invention, R_4 may be C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl, each optionally substituted from one to three times with halogen; or R_2 is H; or R_2 together with the carbon to which it is attached forms a 3, 4 or 5 membered ring. Preferably, R_4 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl.
In accordance with the present invention, R_5 may be C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; C_{1-8} alkyl; unsubstituted C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl); or unsubstituted or substituted Het, said Het substituents being the same or different and being selected from one to three of halo, cyano, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, amido, C_{1-6} alkanoylamino, amino, phenyl or phenylthio, said phenyl or phenyl portion of phenylthio being unsubstituted or substituted by one to three, same or different, substituents selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, amido or phenyl.

In accordance with the present invention, Y may be H, phenyl substituted with nitro, pyridyl substituted with nitro, or C_{1-6} alkyl optionally substituted with cyano, OH or C_{3-7} cycloalkyl; provided that if R_4 or R_5 is H then Yis H.

In accordance with the present invention, B may be H, C_{1-6} alkyl, R_6-(C=O)-, R_6O(C=O)-, R_6-N(R_7)-C(=O)-, R_6-N(R_7)-C(=S)-, R_6SO_2-, or R_6-N(R_7)-SO_2-;

In accordance with the present invention, R_6 may be (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, -OC(O)C_{1-6} alkyl, C_{1-6} alkoxy, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalklyl, each optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (iii) C_{6-10} aryl or

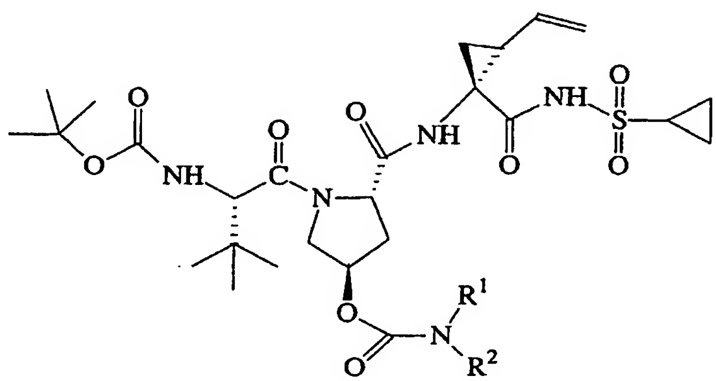
C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl, halogen, nitro, hydroxy, amido, (lower alkyl) amido, or amino optionally substituted with C_{1-6} alkyl; (iv) Het; (v) bicyclo(1.1.1)pentane; or (vi) -C(O)OC_{1-6} alkyl, C_{2-6}alkenyl or C_{2-6} alkynyl. Preferably, R_6 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, C_{1-6} alkoxy; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalklyl; or (iii) C_{6-10} aryl or C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl or halogen. More preferably, R_6 is (i) C_{1-10} alkyl optionally substituted with 1-3 halogen or C_{1-6} alkoxy; or (ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl. Most preferably, R_6 is t-butyl.

In accordance with the present invention, R_7 may be H; C_{1-6} alkyl optionally substituted with 1-3 halogens; or C_{1-6} alkoxy provided R_6 is C_{1-10} alkyl. Preferably, R_7 is H or C_{1-6} alkyl optionally substituted with 1-3 halogens.

The substituents from each grouping may be selected individually and combined in any combination which provides a stable compound in accordance with the present invention. Also, more than one substituent from each group may be substituted on the core group provided there are sufficient available binding sites.

It is preferred that A is $-N(H)SO_mR^5$ wherein R^5 is cyclopropyl. For compounds of the present invention, it is preferred that m is 2. It is also preferred that n is 1.

In a preferred embodiment, compounds of the present invention have the structure of Formula II:



II

and enantiomers, diasteriomers and pharmaceutically acceptable salts thereof, wherein

(a) R^1 is: H, C_{1-6} alkyl, C_{2-10} alkenyl or C_{6-10} aryl, all of which may be substituted with halo, cyano, nitro, C_{1-6} alkoxy, amido, amino or phenyl;

R^2 is:

(i) C_{1-6} alkyl; C_{1-6} alkyl substituted with a carboxy (C_{1-6} alkyl); C_{3-7} cycloalkyl; C_{3-6} cycloalkyl (C_{6-10} aryl); C_{2-10} alkenyl; C_{1-3} alkyl (C_{6-10} aryl); all of which may be substituted from one to three times with halo, C_{1-3} alkyl or C_{1-3} alkoxy; or R^2 is C_{5-9} heterocycle, which may be substituted from one to three times with halo, C_{1-4} alkyl, (C_{1-6} alkyl) carboxy or phenyl; or

(ii) C_{6-10} aryl, which may be substituted from one to three times with the following: halo; C_{1-6} alkyl which itself may be substituted with one to three halo; C_{1-6} alkoxy; nitro; thio (C_{1-6} alkyl); phenyl; C_{1-6} alkanoyl; benzoyl; benzoyl oxime; carboxy; carboxy (C_{1-6} alkyl); (C_{1-6} alkyl) carboxy; phenoxy; (C_{1-6} alkyl) carboxy (C_{1-6} alkyl); or C_{6-10} aryl which may be substituted with a C_{5-9} heterocycle, which heterocycle includes one to three nitrogen, oxygen or sulfur atoms and

which heterocycle itself may be substituted with C_{1-3} alkyl, C_{1-3} alkoxy, $-CF_3$ or (C_{1-3} alkyl) carboxy; or

(b) R^1 and R^2 may join to form a 5 or 6 membered heterocycle, or join to form a 5 or 6 membered heterocycle fused with one or two C_6 aryl groups.

In a preferred embodiment, R^1 is H, C_{1-6} alkyl, C_{2-4} alkenyl or phenyl; and R^2 is phenyl, optionally substituted with C_{1-3} alkyl, one to three chloro or fluoro, phenyl, methoxy, phenoxy, C_{2-4} alkylester, C_{2-6} alkanoyl, nitro, thio(C_{1-4} alkyl) or carboxy.

In another preferred embodiment, R^2 is C_{1-6} alkyl, C_{3-6} cycloalkyl, all of which may be optionally substituted, for example, with a phenyl group.

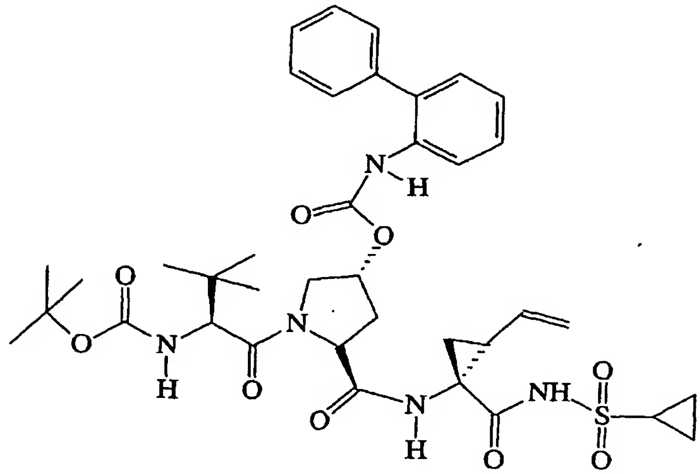
In another preferred embodiment, R^2 is a six membered heterocylic group, optionally substituted with one to three chloro or fluoro atoms or a (C_{1-6} alkyl) carboxy.

In another preferred embodiment, R^2 is an C_{2-4} alkenyl group.

In still another preferred embodiment, R^1 and R^2 form a five or six membered heterocyclic ring, optionally containing oxygen.

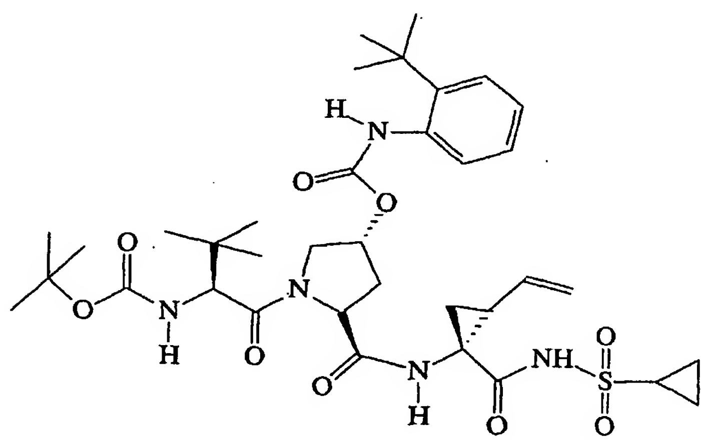
In still another embodiment, R^1 and R^2 form a fused ring structure comprising a five and six membered ring.

In another preferred embodiment is the compound having the Formula III:



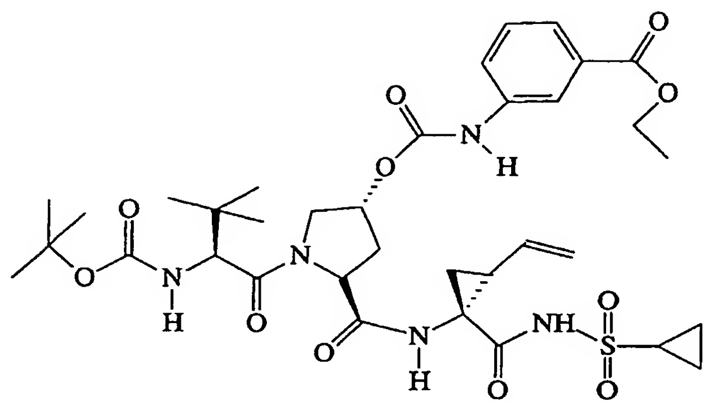
III

In another preferred embodiment is the compound having the Formula IV:



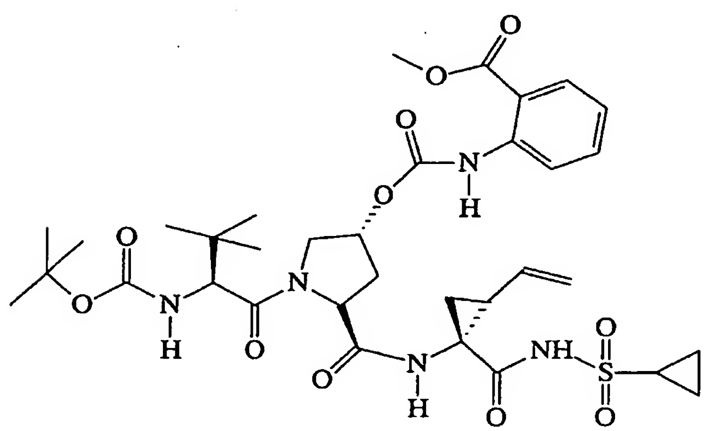
IV

In another preferred embodiment is the compound having the Formula V:



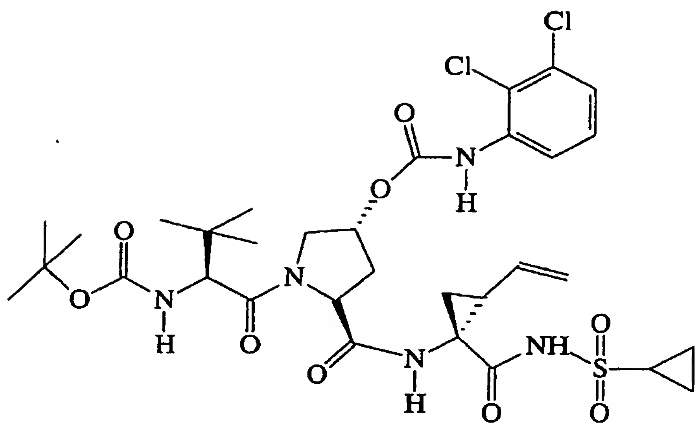
V

In another preferred embodiment is the compound having the Formula VI:



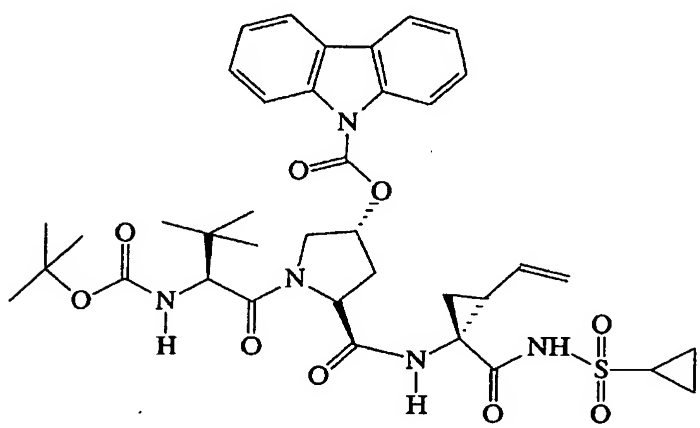
VI

In another preferred embodiment is the compound having the Formula VII:



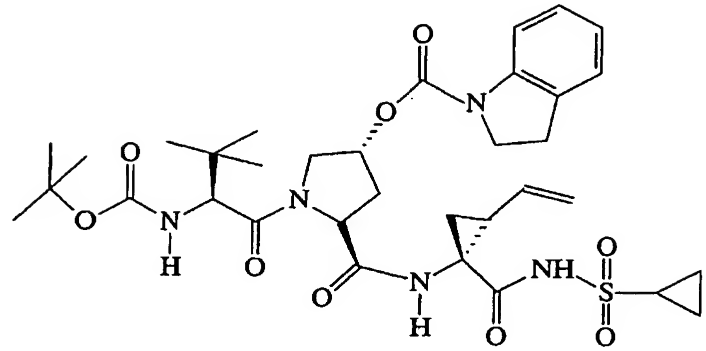
VII

In another preferred embodiment is the compound having the Formula VIII:



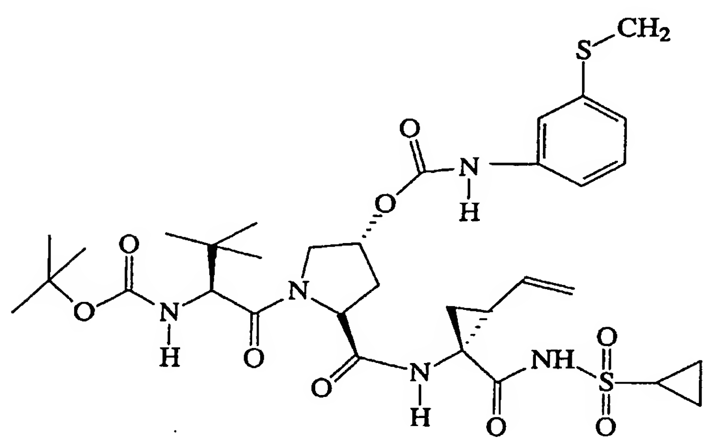
VIII

In another preferred embodiment is the compound having the Formula IX:



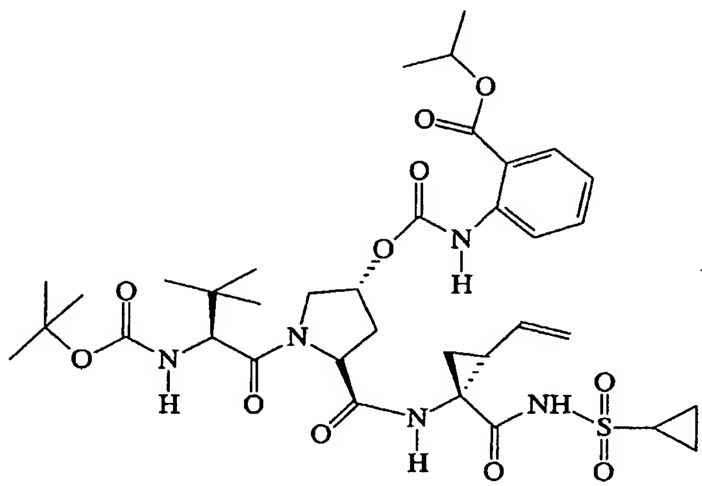
IX

In another preferred embodiment is the compound having the Formula X:



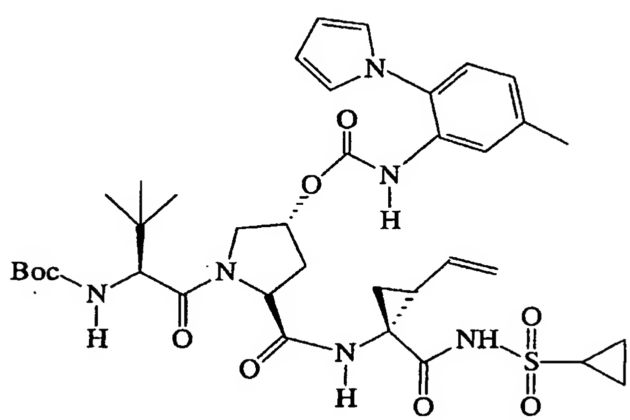
X

In another preferred embodiment is the compound having the Formula XI:



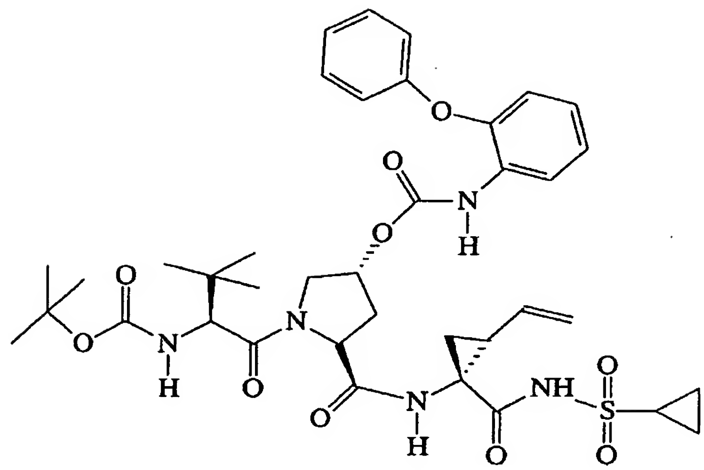
XI

In another preferred embodiment is the compound having the Formula XII:



XII

In another preferred embodiment is the compound having the Formula XIII:



XIII

The compounds of the present invention, when in a basic form, can form salts by the addition of a pharmaceutically acceptable acid. The acid addition salts are formed from a compound of Formula I and a pharmaceutically acceptable inorganic acid, including but not limited to hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, or organic acid such as *p*-toluenesulfonic, methanesulfonic, acetic, benzoic, citric, malonic, fumaric, maleic, oxalic, succinic, sulfamic, or tartaric. Thus, examples of such pharmaceutically acceptable salts include chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartrate.

Salts of an amine group may also comprise quaternary ammonium salts in which the amino nitrogen carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety.

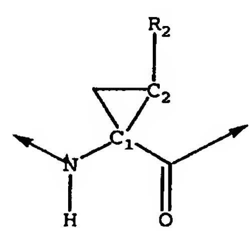
Compounds of the present invention, which are substituted with an acidic group, may exist as salts formed through base addition. Such base addition salts include those derived from inorganic bases which include, for example, alkali metal salts (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts and ammonium salts. In addition, suitable base addition salts include salts of physiologically acceptable organic bases such as

trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bishydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, ethylenediamine, ornithine, choline, N,N'-benzylphenethylamine, chloroprocaine, diethanolamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane and tetramethylammonium hydroxide and basic amino acids such as lysine, arginine and N-methylglutamine. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of the present invention, and their salts, may also exist in the form of solvates with water, for example hydrates, or with organic solvents such as methanol, ethanol or acetonitrile to form, respectively, a methanolate, ethanolate or acetonitrilate. The present invention includes each solvate and mixtures thereof.

In addition, compounds of the present invention, or a salt, solvate or prodrug thereof, may exhibit polymorphism. The present invention also encompasses any such polymorphic form.

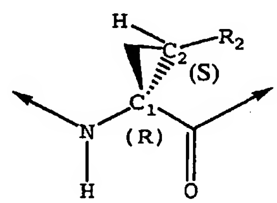
The compounds of the present invention also contain two or more chiral centers. For example, the compounds may include P1 cyclopropyl element of formula



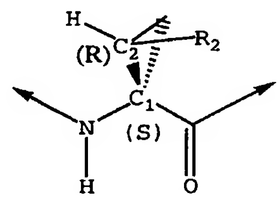
P1

wherein C_1 and C_2 each represent an asymmetric carbon atom at positions 1 and 2 of the cyclopropyl ring. Not withstanding other possible asymmetric centers at other segments of the compounds, the presence of these two asymmetric centers means that

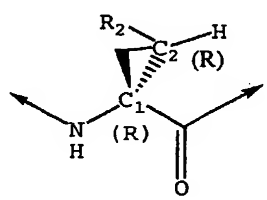
the compounds can exist as racemic mixtures of diastereomers, such as the diastereomers wherein R_2 is configured either syn to the amide or syn to the carbonyl as shown below.



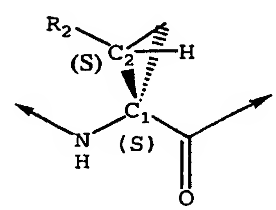
(1R, 2S)
R_2 is syn to carbonyl



(1S, 2R)
R_2 is syn to carbonyl



(1R, 2R)
R_2 is syn to amide



(1S, 2S)
R_2 is syn to amide

The present invention includes both enantiomers and mixtures of enantiomers such as racemic mixtures.

The enantiomers may be resolved by methods known to those skilled in the art, for example, by formation of diastereoisomeric salts which may be separated by crystallization, gas-liquid or liquid chromatography, selective reaction of one enantiomer with an enantiomer-specific reagent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by a separation technique, then an additional step is required to form the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

The compounds of the present invention may be in the form of a prodrug. Simple aliphatic or aromatic esters derived from, when present, acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or (alkoxycarbonyl)oxy)alkyl esters.

Certain compounds of the present invention may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of these compounds and mixtures thereof.

Certain compounds of the present invention may exist in zwitterionic form and the present invention includes each zwitterionic form of these compounds and mixtures thereof.

The starting materials useful to synthesize the compounds of the present invention are known to those skilled in the art and can be readily manufactured or are commercially available.

The compounds of the present invention can be manufactured by methods known to those skilled in the art, see e.p., US Patent No. 6,323,180 and US Patent Appl. 20020111313 A1. The following methods set forth below are provided for illustrative purposes and are not intended to limit the scope of the claimed invention. It will be recognized that it may be preferred or necessary to prepare such a compound in which a functional group is protected using a conventional protecting group then to remove the protecting group to provide a compound of the present invention. The details concerning the use of protecting groups in accordance with the present invention are known to those skilled in the art.

The compounds of the present invention may, for example, be synthesized according to a general process as illustrated in Scheme I (wherein CPG is a carboxyl protecting group and APG is an amino protecting group):

Scheme I

$$\begin{tikzcd}
\mathbf{P1} \arrow[r] & \mathbf{P1}\text{-CPG} + \text{APG-}\mathbf{P2} \arrow[r, "a"] & \text{APG-}\mathbf{P2}\text{-}\mathbf{P1}\text{-CPG} \arrow[d, "b"'] \\
\text{APG-}\mathbf{P3}\text{-}\mathbf{P2}\text{-}\mathbf{P1}\text{-CPG} \arrow[d, "d"'] & & \mathbf{P2}\text{-}\mathbf{P1}\text{-CPG} + \text{APG-}\mathbf{P3} \arrow[ll, "c"'] \\
\text{B-}\mathbf{P3}\text{-}\mathbf{P2}\text{-}\mathbf{P1} \arrow[rr, "e"] & & \text{B-}\mathbf{P3}\text{-}\mathbf{P2}\text{-}\mathbf{P1}\text{-}\mathbf{P1'}
\end{tikzcd}$$

Briefly, the P1, P2, and P3 can be linked by well known peptide coupling techniques. The P1, P2, and P3 groups may be linked together in any order as long as the final compound corresponds to peptides of the invention. For example, P3 can be linked to P2-P1; or P1 linked to P3-P2.

Generally, peptides are elongated by deprotecting the α-amino group of the N-terminal residue and coupling the unprotected carboxyl group of the next suitably N-protected amino acid through a peptide linkage using the methods described. This deprotection and coupling procedure is repeated until the desired sequence is obtained. This coupling can be performed with the constituent amino acids in stepwise fashion, as depicted in Scheme I.

Coupling between two amino acids, an amino acid and a peptide, or two peptide fragments can be carried out using standard coupling procedures such as the azide method, mixed carbonic-carboxylic acid anhydride (isobutyl chloroformate)

method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimide) method, active ester (ρ-nitrophenyl ester, *N*-hydroxysuccinic imido ester) method, Woodward reagent K-method, carbonyldiimidazole method, phosphorus reagents or oxidation-reduction methods. Some of these methods (especially the carbodiimide method) can be enhanced by adding 1-hydroxybenzotriazole or 4-DMAP. These coupling reactions can be performed in either solution (liquid phase) or solid phase.

More explicitly, the coupling step involves the dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the present of a coupling agent to form a linking amide bond. Descriptions of such coupling agents are found in general textbooks on peptide chemistry, for example, M. Bodanszky, "Peptide Chemistry", 2^{nd} rev ed., Springer-Verlag, Berlin, Germany, (1993). Examples of suitable coupling agents are N,N'-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole in the presence of N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-[(3-dimethylamino)propyl]carbodiimide. A practical and useful coupling agent is the commercially available (benzotriazol-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate, either by itself or in the present of 1-hydroxybenzotriazole or 4-DMAP. Another practical and useful coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate. Still another practical and useful coupling agent is commercially available O-(7-azabenzotrizol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate. The coupling reaction is conducted in an inert solvent, e.g. dichloromethane, acetonitrile or dimethylformamide. An excess of a tertiary amine, e.g. diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine or 4-DMAP is added to maintain the reaction mixture at a pH of about 8. The reaction temperature usually ranges between 0 °C and 50 °C and the reaction time usually ranges between 15 min and 24 h.

The functional groups of the constituent amino acids generally must be protected during the coupling reactions to avoid formation of undesired bonds. Protecting groups that can be used are listed, for example, in Greene, "Protective

Groups in Organic Chemistry", John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Synthesis, Biology", Vol. 3, Academic Press, New York (1981), the disclosures of which are hereby incorporated by reference.

The α-amino group of each amino acid to be coupled to the growing peptide chain must be protected (APG). Any protecting group known in the art can be used. Examples of such groups include: 1) acyl groups such as formyl, trifluoroacetyl, phthalyl, and ρ-toluenesulfonyl; 2) aromatic carbamate groups such as benzyloxycarbonyl (Cbz or Z) and substituted bensyloxycarbonyls, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate groups such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate groups such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl groups such as triphenylmethyl and benzyl; 6)trialkylsilyl such as trimethylsilyl; and 7) thiol containing groups such as phenylthiocarbonyl and dithiasuccinoyl.
The preferred α-amino protecting group is either Boc or Fmoc. Many amino acid derivatives suitably protected for peptide synthesis are commercially available.
The α-amino protecting group of the newly added amino acid residue is cleaved prior to the coupling of the next amino acid. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane or in ethyl acetate. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or acetonitrile or dimethylformamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidine in dimethylformamide, but any secondary amine can be used. The deprotection is carried out at a temperature between 0°C and room temperature (rt or RT) usually 20-22°C.

Any of the amino acids having side chain functionalities must be protected during the preparation of the peptide using any of the above-described groups. Those skilled in the art will appreciate that the selection and use of appropriate protecting groups for these side chain functionalities depend upon the amino acid and presence

of other protecting groups in the peptide. The selection of such protecting groups is important in that the group must not be removed during the deprotection and coupling of the α-amino group.

For example, when Boc is used as the α-amino protecting group, the following side chain protecting group are suitable: *p*-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chain of amino acids such as Lys and Arg; acetamidomethyl, benzyl (Bn), or *tert*-butylsulfonyl moieties can be used to protect the sulfide containing side chain of cysteine; bencyl (Bn) ethers can be used to protect the hydroxy containing side chains of serine, threonine or hydroxyproline; and benzyl esters can be used to protect the carboxy containing side chains of aspartic acid and glutamic acid.

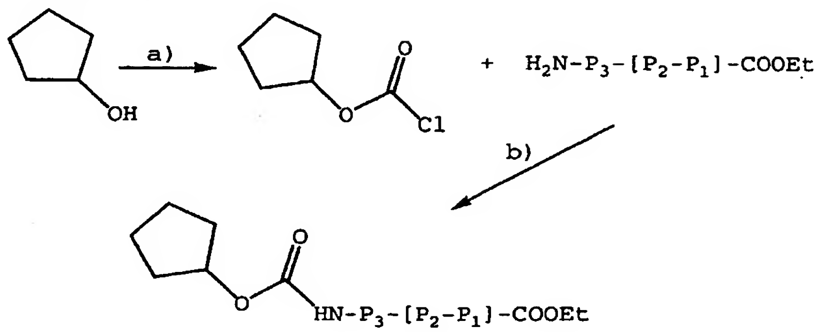
When Fmoc is chosen for the α-amine protection, usually *tert*-butyl based protecting groups are acceptable. For instance, Boc can be used for lysine and arginine, tert-butyl ether for serine, threonine and hydroxyproline, and *tert*-butyl ester for aspartic acid and glutamic acid. Triphenylmethyl (Trityl) moiety can be used to protect the sulfide containing side chain of cysteine.

Once the elongation of the peptide is completed all of the protecting groups are removed. When a liquid phase synthesis is used, the protecting groups are removed in whatever manner is dictated by the choice of protecting groups. These procedures are well known to those skilled in the art.

Further, the following guidance may be followed in the preparation of compounds of the present invention. For example, to form a compound where R_4-C(O)-, R_4-S(O)$_2$,, a protected P3 or the whole peptide or a peptide segment is coupled to an appropriate acyl chloride or sulfonyl chloride respectively, that is either commercially available or for which the synthesis is well known in the art. In preparing a compound where R_4O-C(O)-, a protected P3 or the whole peptide or a peptide segment is coupled to an appropriate chloroformate that is either

commercially available or for which the synthesis is well known in the art. For Boc-derivatives $(Boc)_2O$ is used.

For example:



Cyclopentanol is treated with phosgene to furnish the corresponding chloroformate.

The chloroformate is treated with the desired NH_2-tripeptide in the presence of a base such as triethylamine to afford the cyclopentylcarbamate.

In preparing a compound where R_4-N(R_5)-C(O)-, or R_4-NH-C(S)-, a protected P3 or the whole peptide or a peptide segment is treated with phosgene followed by amine as described in SynLett. Feb 1995; (2); 142-144 or is reacted with the commercially available isocyanate and a suitable base such as triethylamine.

In preparing a compound where R_4-N(R_5)-S(O_2), a protected P3 or the whole peptide or a peptide segment is treated with either a freshly prepared or commercially available sulfamyl chloride followed by amine as described in patent Ger. Offen.(1998), 84 pp. DE 19802350 or WO 98/32748.

The α-carboxyl group of the C-terminal residue is usually protected as an ester (CPG) that can be cleaved to give the carboxylic acid. Protecting groups that can be used include: 1) alkyl esters such as methyl, trimethylsilylethyl and t-butyl, 2) aralkyl esters such as benzyl and substituted benzyl, or 3) esters that can be cleaved

by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters.

The resulting α-carboxylic acid (resulting from cleavage by mild acid, mild base treatment or mild reductive means) is coupled with a $R_1SO_2NH_2$ [prepared by treatment of R_1SO_2Cl in ammonia saturated tetrahydrofuran solution] in the presence of peptide coupling agent such as CDI or EDAC in the presence of a base such as 4-dimethylaminopyridine (4-DMAP) and/or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to incorporate the P1' moiety, effectively assembling the tripeptide P1'-P1-P2-P3-APG. Typically, in this process, 1-5 equivalents of P1' coupling agents are used.

Furthermore, if the P3 protecting group APG is removed and replaced with a B moiety by the methods described above, and the resulting α-carboxylic acid resulting from cleavage (resulting from cleavage by mild acid, mild base treatment or mild reductive means) is coupled with a $R_1SO_2NH_2$ [prepared by treatment of R_1SO_2Cl in ammonia saturated tetrahydrofuran solution or alternative methods described herein] in the presence of peptide coupling agent such as CDI or EDAC in the presence of a base such as 4-dimethylaminopyridine (4-DMAP) and/or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to incorporate the P1' moiety, the tripeptide P1'-P1-P2-P3-B is prepared. Typically, in this process, 1-5 equivalents of P1' coupling agents are used.

Compounds of the present invention can be prepared by many methods including those described in the examples, below, and as described in U.S. Patent No. 6,323,180 and U.S. Patent Application No. 10/001,850 filed on November 20, 2001. The teachings of U.S. Patent No. 6,323,180 and U.S. Patent Application No. 10/001,850 are incorporated herein, in their entirety, by reference.

The present invention also provides compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a pharmaceutically acceptable carrier. Pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, and a

pharmaceutically acceptable carrier, with a pharmaceutically acceptable carrier, e.g., excipient, or vehicle diluent.

The active ingredient, i.e., compound, in such compositions typically comprises from 0.1 weight percent to 99.9 percent by weight of the composition, and often comprises from about 5 to 95 weight percent.

The pharmaceutical compositions of this invention may be administered orally, parenterally or via an implanted reservoir. Oral administration or administration by injection are preferred. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra- articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The details concerning the preparation of such compounds are known to those skilled in the art.

When orally administered, the pharmaceutical compositions of this invention may be administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Other suitable carriers for the above noted compositions can be found in standard pharmaceutical texts, e.g. in "Remington's Pharmaceutical Sciences", 19 th ed., Mack Publishing Company, Easton, Penn., 1995. Further details concerning the design and preparation of suitable delivery forms of the pharmaceutical compositions of the invention are known to those skilled in the art.

Dosage levels of between about 0.01 and about 1000 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.5 and about 250 mg/kg body weight per day of the compounds of the invention are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the peptide. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this invention comprise a combination of a compound of the invention and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage

levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

When these compounds or their pharmaceutically acceptable salts, solvates or prodrugs are formulated together with a pharmaceutically acceptable carrier, the resulting composition may be administered in vivo to mammals, such as man, to inhibit HCV NS3 protease or to treat or prevent HCV virus infection. Such treatment may also-be achieved using the compounds of this invention in combination with agents which include, but are not limited to: immunomodulatory agents, such as interferons; other antiviral agents such as ribavirin, amantadine; other inhibitors of HCV NS3 protease; inhibitors of other targets in the HCV life cycle such as helicase, polymerase, metalloprotease, or internal ribosome entry site; or combinations thereof. The additional agents may be combined with the compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered to a mammal as part of a multiple dosage form.

Accordingly, another aspect of this invention provides methods of inhibiting HVC NS3 protease activity in patients by administering a compound of the present invention or a pharmaceutically acceptable salt or solvate thereof, wherein the substituents are as defined above.

In a preferred embodiment, these methods are useful in decreasing HCV NS3 protease activity in the patient. If the pharmaceutical composition comprises only a compound of this invention as the active component, such methods may additionally comprise the step of administering to said patient an agent selected from an immunomodulatory agent, an antiviral agent, a HCV protease inhibitor, or an inhibitor of other targets in the HCV life cycle such as, for example, helicase, polymerase, or metalloprotease. Such additional agent may be administered to the patient prior to, concurrently with, or following the administration of the compounds of this invention.

In an alternate preferred aspect, these methods are useful for inhibiting viral replication in a patient. Such methods can be useful in treating or preventing HCV disease.

The compounds of the invention may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms.

The compounds of this invention may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

Examples

The specific examples that follow illustrate the syntheses of the compounds of the instant invention, and are not to be construed as limiting the invention in sphere or scope. The methods may be adapted to variations in order to produce compounds embraced by this invention but not specifically disclosed. Further, variations of the methods to produce the same compounds in somewhat different manner will also be evident to one skilled in the art.

Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300 or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (W.C. Still et al., J. Org. Chem.(1978) 43, 2923).

All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector and Mass

Spectrometry (MS) data were determined with a Micromass Platform for LC in electrospray mode (ES+).

Unless otherwise noted, each compound was analyzed by LCMS, using one of the following methodologies and conditions (listed for each compound whereas LC-MS A corresponds to Method A, etc.):

Columns: Method A: YMC ODS-A C18 S7 (3.0 x 50 mm)

Method B: YMC ODS-A (5.0 x 30 mm)

Method C: Xterra C18 S7 (3.0 x 50mm)

Method D: YMC C18 S5 (4.6 x 50 mm)

Method E: YMC C18 S5 (4.6 x 33mm)

Method F: Xterra C18 S7 (3.0 x 50mm)

Method G: Xterra MS C18 (4.6 x 30mm)

Method H: Xterra ODS S7 (3.0 x 50mm)

Gradient: 100% solvent A/ 0% solvent B to 0% solvent A/ 100% solvent B

Gradient time: 1.5 min. (H), 2 min. (D), 3 min. (A, B, C, G), 4 min. (F), 15 min. (E)

Hold Time: 1 min.

Flow Rate: 4 mL/min. (A-C, E-G), 5 mL/min. (D,H)

Detector Wavelength: 220 nm.

Solvents (A-D, F-H): Solvent A: 10% MeOH/ 90% water/ 0.1% TFA.

Solvent B: 90% MeOH/ 10% water/ 0.1% TFA.

Solvents (E): Solvent A: 10% MeOH/ 90% water/ 0.2% H_3PO_4

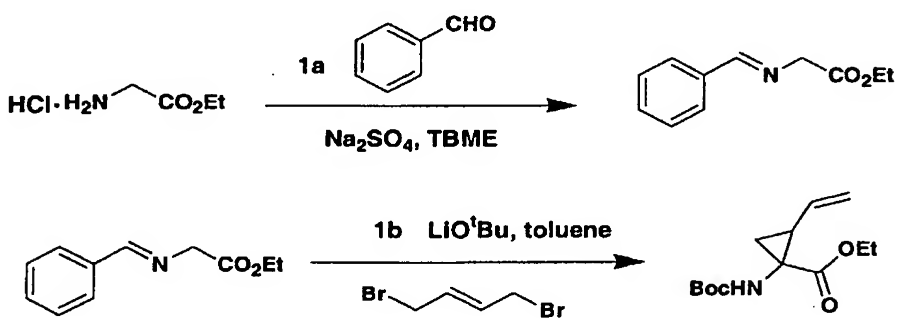
Solvent B: 90% MeOH/ 10% water/ 0.2% H_3PO_4

In the preparation of the following compounds, it has been discovered that a partial epimerization occurs during preparation. Consequently, small amounts of diastereomers most likely epimeric at the P2 proline chiral center may be present.

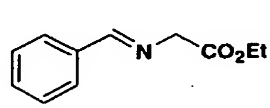
The compounds and chemical intermediates of the present invention, described in the following examples, were prepared according to the following methods.

Examples 1-3 describe the intermediates used for the formation of the tripeptides described in Example 4 and specifically Compounds 1-68.

Example 1: Preparation of a P1 intermediate, racemic *N*-Boc-(1R/2S)/(1S/2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester.



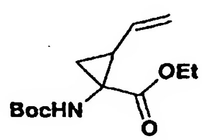
Step 1a: Preparation of *N*-benzyl imine of glycine ethyl ester, shown below.



Glycine ethyl ester hydrochloride (303.8 g, 2.16 mole) was suspended in tert-butylmethyl ether (1.6 L). Benzaldehyde (231 g, 2.16 mole) and anhydrous sodium sulfate (154.6 g, 1.09 mole) were added and the mixture cooled to 0 °C using an ice-

water bath. Triethylamine (455 mL, 3.26 mole) was added dropwise over 30 min and the mixture stirred for 48 h at rt. The reaction was then quenched by addition of ice-cold water (1 L) and the organic layer was separated. The aqueous phase was extracted with *tert*-butylmethyl ether (0.5 L) and the combined organic phases washed with a mixture of saturated aqueous $NaHCO_3$ (1 L) and brine (1 L). The solution was dried over $MgSO_4$, concentrated in vacuo to afford 392.4 g of the *N*-benzyl imine product as a thick yellow oil that was used directly in the next step. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, *J*=7.1 Hz, 3H), 4.24 (q, *J*=7.1 Hz, 2H), 4.41 (d, *J*=1.1 Hz, 2H), 7.39-7.47 (m, 3H), 7.78-7.81 (m, 2H), 8.31 (s, 1H).

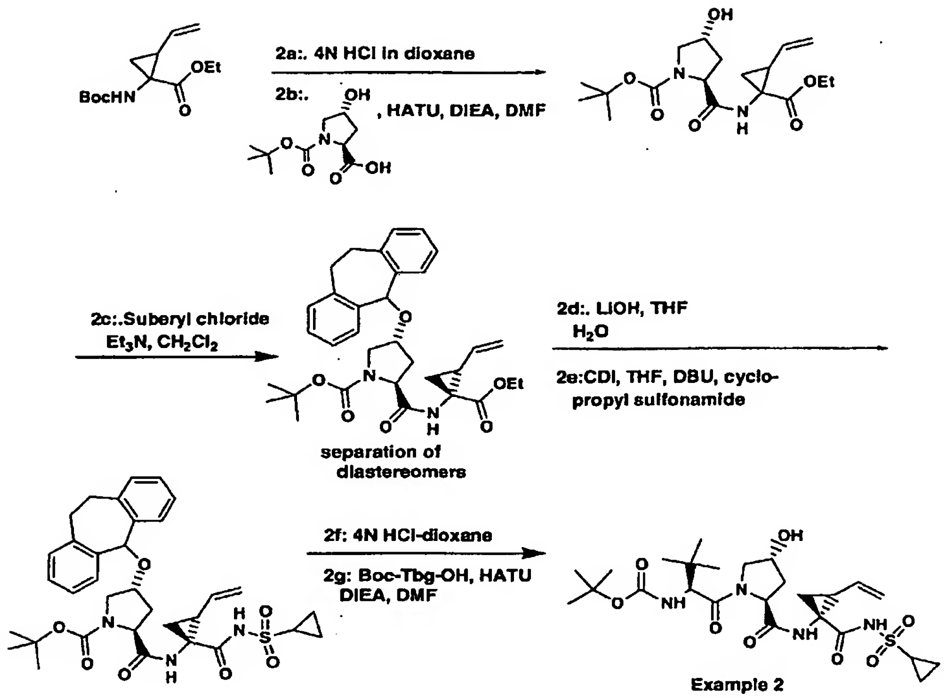
Step 1b: Preparation of racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester



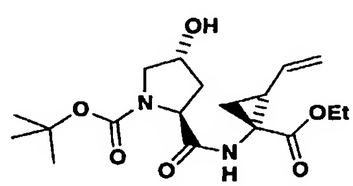
To a suspension of lithium tert-butoxide (100 g, 1.25 mol) in dry toluene (1.0 L), was added dropwise a mixture of the *N*-benzyl imine of glycine ethyl ester (119.3 g, 0.625 mol) and *trans*-1,4-dibromo-2-butene (126.3 g, 0.594 mol) in dry toluene (0.8 L) over 60 min. After completion of the addition, the deep red mixture was quenched by addition of water (1 L) and *tert*-butylmethyl ether (TBME, 1 L). The aqueous phase was separated and extracted a second time with TBME (1 L). The organic phases were combined, 1 N HCl (1.3 L) was added and the mixture stirred at room temperature for 2 h. The organic phase was separated and extracted with water (1.0 L). The aqueous phases were then combined, saturated with salt (1000 g), TBME (1 L) was added and the mixture cooled to 0 °C. The stirred mixture was then basified to pH 14 by the dropwise addition of 10 N NaOH, the organic layer separated, and the aqueous phase extracted with TBME (2 x 500 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a volume of 1L. To this solution of free amine, was added di-*tert*-butyldicarbonate (124.7 g, 0.714 mol) and the mixture stirred 4 days at rt. Additional di-*tert*-butyldicarbonate (65.5 g, 0.375

mol) was added to the reaction, the mixture refluxed for 3 h, and was then allowed cool to room temperature overnight. The reaction mixture was dried over $MgSO_4$ and concentrated *in vacuo* to afford 200 g of crude material. This residue was purified by flash chromatography (2.5 Kg of SiO_2, eluted with 1% to 2% $MeOH/CH_2Cl_2$) to afford 72.5 g (48%) of racemic *N*-Boc-(*1R*,*2S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as a yellow oil which solidified while sitting in the refrigerator. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, *J*=7.1 Hz, 3H), 1.46 (s, 9H), 1.43-1.49 (m, 1H), 1.76-1.82 (br m, 1H), 2.14 (q, *J*=8.6 Hz, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 5.12 (dd, *J*=10.3, 1.7 Hz, 1H), 5.25 (br s, 1H), 5.29 (dd, *J*=17.6, 1.7 Hz, 1H), 5.77 (ddd, *J*=17.6, 10.3, 8.9 Hz, 1H).

Example 2: Preparation of BocNH-P3(t-BuGly)-P2(Hyp)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane:



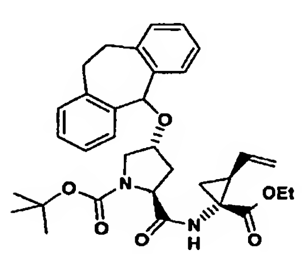
Step 2a and step 2b: Preparation of BocNH-P2(Hyp)-P1(1*R*,2*S*)/(*1S/2R)* VinylAcca)OEt, shown below:



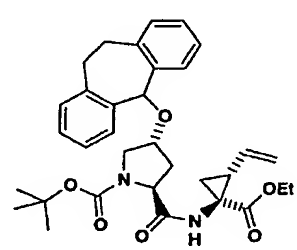
Racemic *N*-Boc-(1R/2S)/(1S/2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (18.75g) was dissolved in 4N HCl-dioxane (87 mL, 345 mmol). The solution was stirred for 1.5 hours and then concentrated *in vacuo* to yield the HCl salt of (1R/2S)/(1S/2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (14g) as an orange foam/oil which was taken on to the next step without purification. The HCl salt of (1R/2S)/(1S/2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (14.07g) was dissolved in 1.30 L dry acetonitrile, under a nitrogen atmosphere, in a

5-litre flask equipped with a mechanical stirrer. The solution was cooled in a water-ice bath to 5°C. Boc-Hyp-OH (34.0g, 147 mmol) was added and the mixture allowed to stir for 15 minutes. Diisopropylethylamine (61.4 mL, 353 mmol), acetonitrile (100 mL) and finally HATU (41.9g, 110 mmol) was added to the reaction. After 27 hours, the mixture was concentrated *in vacuo* to a thick orange oil which was immediately diluted with 1.2 L ethyl acetate and divided into three 400 mL portions. Each 400 mL portion was washed with 500 mL water, 500 mL 1N sodium bicarbonate solution, 500 mL 1N hydrochloric acid solution, 500 mL 1N sodium bicarbonate solution and 500 mL brine. The organics were combined and dried over sodium sulfate and concentrated *in vacuo*. The crude was dissolved in a minimal amount of methylene chloride and gravity filtered through a plug of silica (1 kg) eluting with 2:1 ethyl acetate: hexanes to yield the titled product 17.9g (66%) as an off-white foam: ^{1}H NMR (d_4-MeOH, 500Mz, 55^{0}C) δ 5.74 (m, 1H), 5.28 (dd, 1H, J=17, 1.6 Hz), 5.10 (d, 1H, J=10.4 Hz), 4.39 (m, 1H), 4.26 (t, 1H, J=7.7 Hz), 4.13 (m, 2H), 3.57 (ddd, 1H, 4.55, 4.45, 3.5 Hz), 3.44 (m, 1H), 2.21 (m, 1H), 2.18 (dt, 1H, 9.1, 8.5 Hz), 2.10 (m, 1H), 1.77 (bm, 2H), 1.42 and 1.44 (9H, s, from diastereomers), 1.22 (t, 3H, J=7.1 Hz). LC-MS H (retention time: 1.09 ; MS m/z 369 (M+H).

Step 2c: Preparation of BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-OEt, and separation of resulting diastereoisomers as described below:



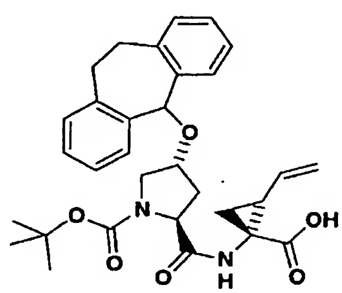
Desired isomer:
Stereochemistry in cyclopropane ring (1R, 2S),
higher Rf compound on TLC
first eluent during flash chrom. as described below



Undersired isomer:
Stereochemistry in cyclopropane ring (1S, 2R), lower Rf compound

BocNH-P2(Hyp)-P1(1*R*,2*S*)/(1S/2R*)* VinylAcca)-OEt (54.715g) was dissolved in 500 mL methylene chloride. To this solution was added in succession suberyl chloride (37.39g, 163 mmol) and triethylamine (41.4 mL, 297 mmol) and the reaction was stirred under nitrogen for 39 hours. The mixture was then washed with 2 x 600 mL water and 2 x 600 mL brine. The organic layer was then filtered through a plug of silica gel slurried with methylene chloride. The product fractions were concentrated to yield a yellow foam which was purified by a Biotage Flash150 silica column by loading in 400 mL diethyl ether and elution with 3:1 hexanes: ethyl acetate. The fractions containing product were concentrated *in vacuo* to yield the titled product 21.67g (26%) as the higher Rf diastereomer: ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.33 (m, 2H), 7.15 (m, 6H), 5.73 (m, 1H), 5.45 (m, 1H), 5.28 (m, 1H), 5.08 (m, 1H), 4.21 (m, 2H), 4.07 (m, 3H), 3.48 (m, 4H), 2.94 (bm, 2H), 2.35 (bm, 1H), 2.14 (m, 1H), 1.99 (m, 1H), 1.71 (m, 1H), 1.38 and 1.40 (s, 9H, conformers), 1.31 (m,1 H), 1.19 and 1.22 (t, 3H, conformers). LC-MS D (retention time: 1.94 ; MS m/z 561 (M+H).

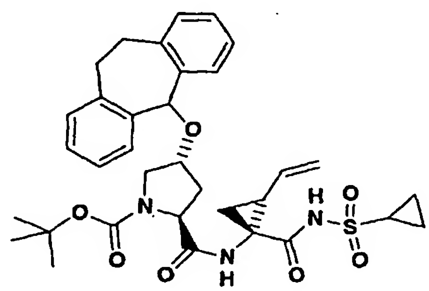
Step 2d: Preparation of BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-OH, shown below



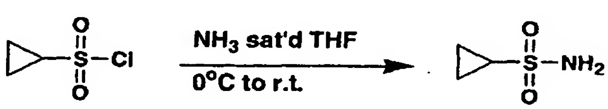
BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-OEt (24.02g) was dissolved in 50 mL methanol and 100 mL tetrahydrofuran under an atmosphere of nitrogen. A solution of 1N NaOH (51 mL, 51.0 mmol) was then added slowly to the mixture. The solution was stirred for 21 hours and then 51 mL of 1N hydrochloric acid solution was added portionwise. The mixture was concentrated *in vacuo* and left on the vacuum pump overnight. After 16 hours, the crude was dissolved in 100 mL ethyl acetate and filtered through a two liter fritted funnel containing 42mm of silica

gel. The product was eluted with ethyl acetate to yield the titled product 22.4g (98%) as a white solid: ^{1}H NMR (DMSO-d_6, 500Mz) δ 12.55 (bs, 1H), 7.36 (m, 2H), 7.18 (m, 6H), 5.74 (m, 1H), 5.59 (bm, 1H), 5.22 (d, 1H, 16.8 Hz), 5.05 (d, 1H, J=11 Hz), 4.07 (m, 2H), 3.36-3.43 (m, 4H), 3.00 (bm, 2H), 2.30 (m, 1H), 1.89 (m, 1H), 1.55 (m, 1H), 1.31 and 1.34 (s, 9H rotomers), 1.20 (m, 1H). LC-MS E (retention time: 3.09 ; MS m/z 533 (M+H).

Step 2e: Preparation of BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane:

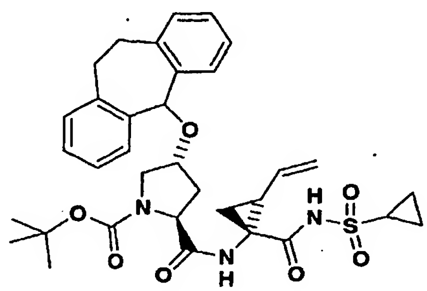


Preparation of cyclopropyl sulfonamide moiety for use in step 2e:



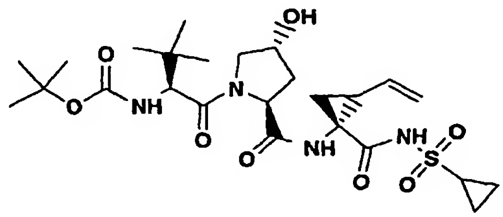
To a solution of 20 mL THF cooled to 0°C was bubbled in gaseous ammonia until saturation was reached. To this solution was added 2g (5.69 mmol) of cyclopropylsulfonyl chloride (purchased from Array Biopharma). The solution was warmed to room temperature over two hours and the crude solution was filtered through a plug of silica gel eluting the product with ethyl acetate. The fractions were concentrated *in vacuo* to yield 1.70 g (99%) of cyclopropyl sulfonamide as a white solid: ^{1}H NMR (d_4-MeOH, 500MHz) δ 0.94-1.07 (m, 4H), 2.52-2.60 (m, 1H).

Preparation of BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane shown below:



BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-OH (9.7 g) was dissolved in 50 mL tetrahydrofuran in a 250 mL round bottom flask under a nitrogen atmosphere. Carbonyldiimidazole (3.54g, 21.9 mmol) was then added to the solution. The mixture was heated to 80°C for one hour and then removed from the heat but allowed to continue stirring for an additional 1.75 hours. Cyclopropyl sulfonamide (4.33g, 45.5 mmol) was added to the solution followed by DBU (5.45 mL, 36.4 mmol) and stirred for 16 hours. The reaction was concentrated under high vacuum and then diluted with 600 mL ethyl acetate. The organic layer was washed with 2 x 300 mL 1N HCl. The HCl layers were back extracted with 100 mL ethyl acetate and this was combined with the other organic layer. The combined organic layers were then washed with 2 x 300 mL water and 2 x 300 mL brine. The solution was dried over sodium sulfate and concentrated *in vacuo*. The oil was then dissolved in methylene chloride and gravity filtered through a silica plug (67mm x 33mm) eluting with 1:1 ethyl acetate hexanes to give 8.66g (75%) of an off-white crystalline solid: ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.34 (m, 2H), 7.18 (m, 6H), 5.75 (m, 1H), 5.47 (bm, 1H), 5.30 (d, 1H, J=17 Hz), 5.12 (d, 1H, J=10.4 Hz), 4.21 (m, 2H), 3.49 (m, 3H), 3.39 (dd, 11.6, 3.7Hz), 2.93 (m, 2H), 2.18-2.23 (m, 2H), 1.82-1.91 (m, 2H), 1.42 (s, 9H), 1.36-1.42 (m, 4H), 1.02-1.15 (m, 2H). LC-MS A (retention time: 2.83 ; MS m/z 658 (M+Na).

Step 2f and step 2g: Preparation of BocNH-P3(t-BuGly)-P2(Hyp)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane:



BocNH-P2(Hyp(O-suberyl))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$- Cyclopropane (8.66g, 13.6 mmol) was treated with 4N HCl in dioxane (34 mL) and stirred for 1.5 hours. The reaction was then diluted with diethyl ether (100 mL) and the prepicitate collected on a Buchner filter funnel to yield 4.94g of a pale yellow foam which was taken to the next step without further purification. The HCl salt of P2(Hyp)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$- Cyclopropane (4.94g, 13.0 mmol) was then dissolved in dimethylformamide (40 mL) under an atmosphere of nitrogen. The solution was cooled in a water-ice bath to 2°C. N-Boc-*L*-tert-leucine (3.16g, 13.7 mmol), freshly distilled diethylisopropylamine (9.0 mL, 52.0 mmol and HATU (5.44g, 14.3 mmol) were added. The reaction was stirred for 18.5 hr, at which time it was concentrated *in vacuo* to ~15 mL and diluted with ethyl acetate (350 mL). The organic layer was then washed with water (200 mL), 1N hydrochloric acid solution (2 x 350 mL) and brine (2 x 350 mL) and dried over sodium sulfate. The solution was concentrated to ~20 mL and then gravity filtered through a plug of silica eluting with 1:1 ethyl acetate: hexanes to yield the titled product 4.78g (66%) as a white solid: ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 6.65 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.31 (d, J=17.1 Hz, 1 H), 5.13 (d, J=10.4 Hz, 1 H), 4.49 (s, 1 H), 4.37 (m, 1 H), 4.30 (d, J=9.5 Hz, 1 H), 3.81 (m, 2 H), 2.93 (m, 1 H), 2.23 (q, J=8.9 Hz, 1 H), 2.12 (dd, J=13.1 Hz, 7.0 Hz, 1 H), 1.97 (m, 1 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.44 (s, 9 H), 1.40 (m, 1 H), 1.23 (t, J=7.0 Hz, 2 H), 1.07 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.20 ; MS m/z 557 (M+H).

Example 3: Preparation of isocyanates and carbamoyl chlorides for use in Example 4

The isocyanates and carbamyl chlorides used in Example 4 were commercially available except those shown in Table 1 which were synthesized by the following methods.

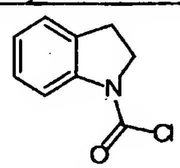
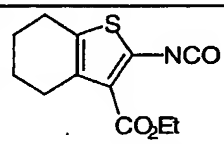
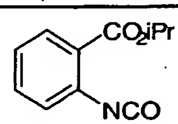
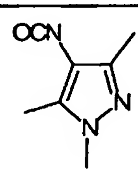
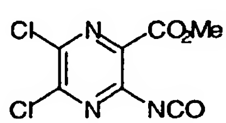
Procedures for formation of isocyanates and carbamyl chlorides (see Table 1):

Method A: A solution of indoline (2 mL, 17.8 mmol) dissolved in THF (25 mL) was added to a precooled solution of phosgene (20%) in toluene (38 mL), Et_3N (2.5 mL) in toluene (30mL) at –78°C. After stirring three hours at –78°C, the solution was warmed under a stream of N_2 and then concentrated *in vacuo*. The product was recrystallized from ethyl acetate/hexanes.

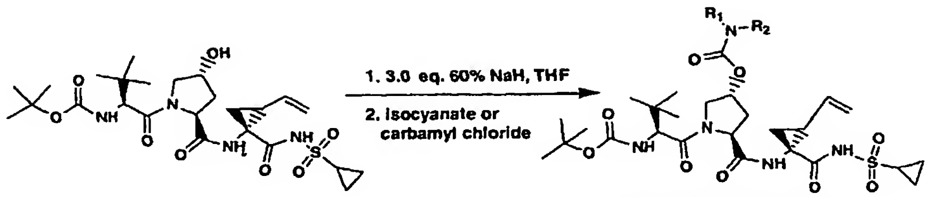
Method B: The amine (1.0eq) was supsended or dissolved in toluene (0.5M). Phosgene (20%) in toluene (4.0 eq.) was then added and the mixture heated for two hours. The reaction was then cooled and the product was filtered or precipitated by hexanes or ethyl acetate, then filtered and dried under vacuum.

Method C: Methyl-3-amino-5,6-dichloro 2-pyrazine carboxylate (3g, 13.5 mmol) was suspended in toluene (7 mL) and heated to 110°C. Then a solution of oxalyl chloride (4.7 mL) in toluene (14 mL) was added dropwise via syringe. After 2-4 hours, reaction was cooled to room temperature and concentrated *in vacuo* to a brown-black oil. The product was distilled (122^{0}C, 0.1mm) to yield a yellow solid.

Table 1

Isocyanate/ Carbamyl Chloride	Method	Temp.	Time	Precipitation Method	Yield
	A	see method details		recrystallized	5%
	B	80°C	4h	EtOAc	46%
	B	80°C	2h	Hexanes	89%
	B	100°C	2h	filtered	<10%
	C	see method details		n/a	46%

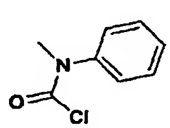
Example 4: General procedure for the preparation of tripeptide P2 -carbamates (Compounds 1-68) as shown below:



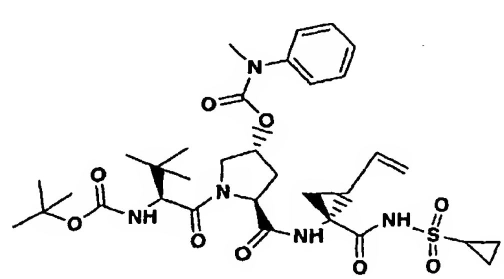
Tripeptide P2 carbamates

Representative procedure to make tripeptide P2-carbamates (BocNH-P3(t-BuGly)-P2(Hyp(O-CO-NR^{1}R^2)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$.Cyclopropane), Compounds 1-68 , using isocyanates or carbamyl chlorides:

BocNH-P3(t-BuGly)-P2(Hyp)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$.Cyclopropane (80 mgs,0.144 mmol) was dissolved in 500 microliters of tetrahydrofuran and the solution cooled to 2°C in an ice/water bath. To this cooled mixture was added 60% sodium hydride in mineral oil (18 mgs, 0.431 mmol) followed by the isocyanate or carbamyl chloride (1.1 equivalents). After stirring 2 hours, the cold bath was removed and then mixture allowed to stir for another 2 hours before quenching with saturated ammonium chloride solution. The reaction was then diluted with 30 mL ethyl acetate and then washed with 30 mL 1N HCl and 30 mL brine. The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The oil/solid was diluted with 3 mL methylene chloride and filtered through a 50 mm by 1½" slurry of silica gel and 1-1 hexanes-ethyl acetate. Further elution with ethyl acetate yields the tripeptide P2-carbamates:



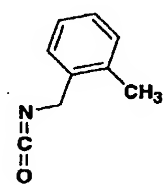
Reagent employed for preparation of Compound 1



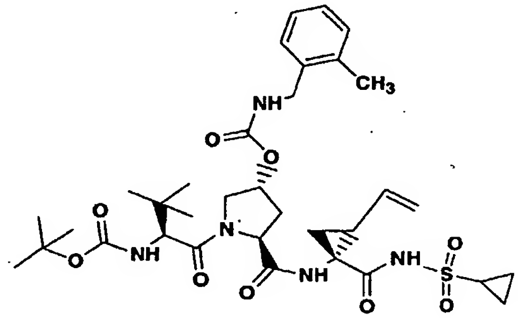
Compound 1

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N-methyl,N-phenyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.34 (m, 2 H), 7.21 (t, J=7.3 Hz, 3 H), 6.63 (d, J=7.6 Hz, 1 H), 5.78 (m, 1 H), 5.31 (s, 1 H), 5.23 (d, J=17.1 Hz, 1 H), 5.06 (d, J=9.8 Hz, 1 H), 4.25 (d, J=9.2 Hz, 1 H), 4.21 (m, 2 H), 3.90 (m, 1 H), 3.26 (s, 3 H), 2.85 (m, 1 H), 2.12 (m, 3 H), 1.82 (m, 1 H), 1.43 (m, 1 H), 1.40 (s, 9 H), 1.15 (m, 2 H), 1.02 (s, 9 H), 0.96 (m, 2 H). LC-MS A (retention time: 2.40 ; MS m/z 691 (M+H).



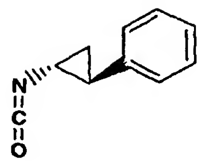
Reagent employed for preparation of Compound 2



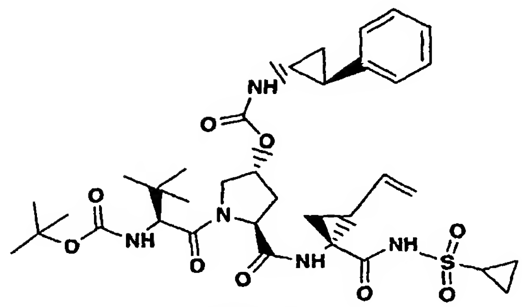
Compound 2

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-methylbenzyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(94%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.21 (s, 1 H), 7.13 (s, 3 H), 6.63 (d, J=9.2 Hz, 1 H), 5.77 (m, 1 H), 5.32 (s, 1 H), 5.30 (d, J=18.3 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.35 (m, 1 H), 4.25 (m, 3 H), 4.07 (m, 1 H), 3.93 (m, 1 H), 2.91 (m, 1 H), 2.34 (m, 1 H), 2.30 (s, 3 H), 2.23 (m, 1 H), 2.13 (m, 1 H), 1.85 (m, 1 H), 1.43 (s, 9 H), 1.35 (s, 1 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.65 ; MS m/z 704 (M+H).



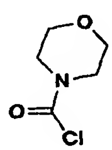
Reagent employed for preparation of Compound 3



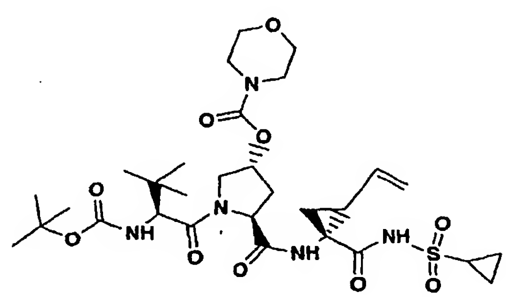
Compound 3

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2(*trans*)-phenylcyclopropyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(93%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.23 (, 2 H), 7.12 (m, 3 H), 5.77 (m, 1 H), 5.30 (d, J=15.9 Hz, 2 H), 5.12 (d, J=10.1 Hz, 1 H), 4.35 (m, 1 H), 4.26 (d, J=9.5 Hz, 1 H), 4.10 (m, 2 H), 3.93 (m, 1 H), 2.92 (s, 1 H), 2.68 (m, 1 H), 2.33 (m, 1 H), 2.21 (m, 1 H), 2.13 (m, 1 H), 2.03 (, 1 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.45, 1.42 (s, 10 H, from two isomers), 1.23 (m, 2 H), 1.05 (m, 2 H), 1.01 (s, 9 H), 0.88 (m, 2 H). LC-MS A (retention time: 2.69 ; MS m/z 716 (M+H).

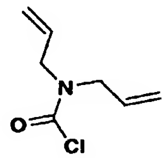


Reagent employed for preparation of Compound 4

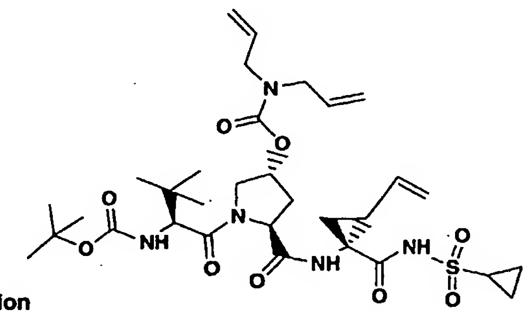


Compound 4

BocNH-P3(t-BuGly)-P2(Hyp(O-CO-(4-morpholino)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (58%): LC-MS A (retention time: 2.31 ; MS m/z 670 (M+H).



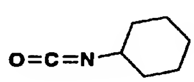
Reagent employed for preparation of Compound 5



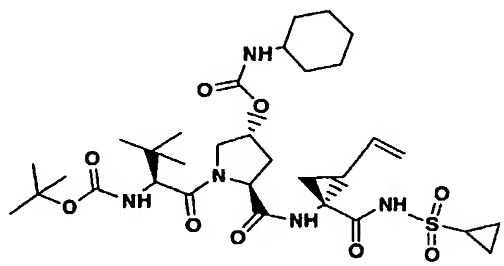
Compound 5

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-diallyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(98%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 6.63 (d, J=9.5 Hz, 1 H), 5.76 (m, 3 H), 5.30 (m, 2 H), 5.11 (m, 5 H), 4.33 (dd, J=10.7 Hz, 7.0 Hz, 1 H), 4.24 (d, J=9.5 Hz, 1 H), 4.12 (d, J=11.9 Hz, 1 H), 3.87 (m, 3 H), 3.79 (m, 2 H), 2.92 (m, 1 H), 2.33 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.22 (q, J=8.8 Hz, 1 H), 2.13 (m, 1 H), 1.86 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (s, 10 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.62 ; MS m/z 680 (M+H).



Reagent employed for preparation of Compound 6



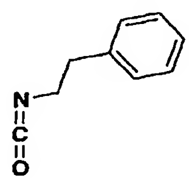
Compound 6

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-cyclohexyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

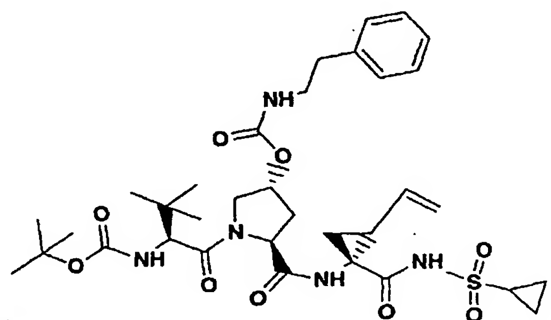
(31%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.00 (d, J=7.6 Hz, 1 H), 6.64 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.31 (d, J=18.6 Hz, 1 H), 5.27 (s, 1 H), 5.12 (d, J=11.9 Hz, 1 H),

4.33 (m, 1 H), 4.25 (d, J=9.5 Hz, 1 H), 4.03 (m, 1 H), 3.92 (m, 1 H), 3.34 (s, 1 H), 2.93 (m, 1 H), 2.30 (m, 1 H), 2.23 (q, J=8.6 Hz, 1 H), 2.11 (m, 1 H), 1.86 (m, 3 H), 1.72 (m, 2 H), 1.44 (s, 10 H), 1.31 (m, 2 H), 1.24 (m, 2 H), 1.17 (m, 4 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.67 ; MS m/z 682 (M+H).

Compound 7



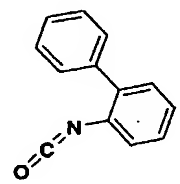
Reagent employed for preparation of Compound 7



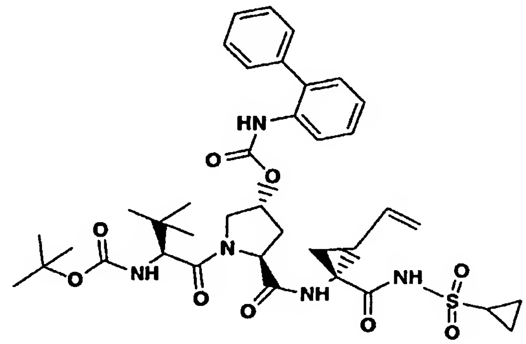
Compound 7

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-phenethyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(19%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.27 (t, J=7.6 Hz, 2 H), 7.19 (d, J=7.6 Hz, 3 H), 5.77 (m, 1 H), 5.30 (d, J=17.4 Hz, 1 H), 5.26 (s, 1 H), 5.13 (d, J=10.4 Hz, 1 H), 4.32 (m, 1 H), 4.26 (d, J=9.5 Hz, 1 H), 4.04 (m, 1 H), 3.92 (m, 1 H), 3.30 (m, 2 H), 2.93 (m, 1 H), 2.76 (m, 2 H), 2.26 (m, 2 H), 2.10 (m, 1 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.43 (s, 9 H), 1.33 (s, 1 H), 1.24 (m, 2 H), 1.07 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.65 ; MS m/z 704 (M+H).



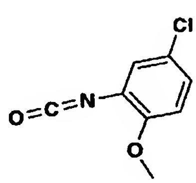
Reagent employed for preparation of Compound 8



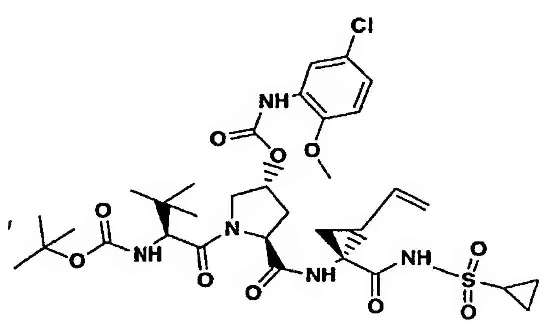
Compound 8

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-biphen-2-yl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(83%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.67 (m, 1 H), 7.44 (m, 2 H), 7.35 (m, 4 H), 7.25 (m, 2 H), 6.62 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.31 (d, J=17.4 Hz, 1 H), 5.26 (s, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.25 (m, 2 H), 4.05 (t, J=6.7 Hz, 1 H), 3.91 (m, 1 H), 2.92 (m, 1 H), 2.21 (m, 2 H), 2.09 (m, 1 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.42 (m, 1 H), 1.39 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.06 (m, 2 H), 1.00 (s, 9 H). LC-MS A (retention time: 3.00 ; MS m/z 752 (M+H).



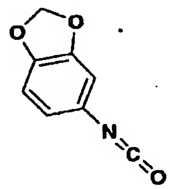
Reagent employed for preparation of Compound 9



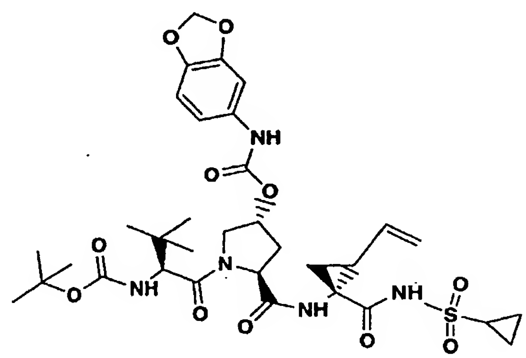
Compound 9

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-chloro-2-methoxy-phenyl)))) - P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(60%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.98 (s, 1 H), 6.99 (d, J=8.5 Hz, 1 H), 6.92 (d, J=8.9 Hz, 1 H), 6.63 (d, J=9.2 Hz, 1 H), 5.77 (m, 1 H), 5.40 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=11.6 Hz, 1 H), 4.40 (dd, J=9.8 Hz, 7.3 Hz, 1 H), 4.24 (t, J=9.2 Hz, 2 H), 3.96 (d, J=11.9 Hz, 1 H), 3.84 (s, 3 H), 2.93 (m, 1 H), 2.42 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.23 (m, 2 H), 1.87 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.43 (m, 1 H), 1.36 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.76 ; MS m/z 740 (M+H).



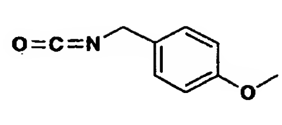
Reagent employed for preparation of Compound 10



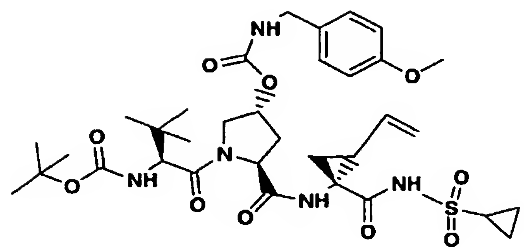
Compound 10

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-Benzo[1,3]dioxol-5-yl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(70%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.08 (s, 1 H), 6.76 (m, 1 H), 6.70 (d, J=8.6 Hz, 1 H), 6.63 (d, J=9.5 Hz, 1 H), 5.89 (s, 2 H), 5.77 (m, 1 H), 5.37 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.39 (t, J=8.0 Hz; 1 H), 4.27 (d, J=9.5 Hz, 1 H), 4.16 (d, J=12.2 Hz, 1 H), 3.95 (dd, J=11.3 Hz, 3.4 Hz, 1 H), 2.93 (m, 1 H), 2.40 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.21 (m, 2 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.43 (m, 1 H), 1.39 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.05 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.56 ; MS m/z 720 (M+H).



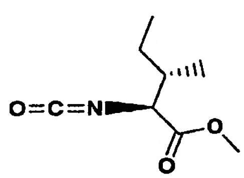
Reagent employed for preparation of Compound 11



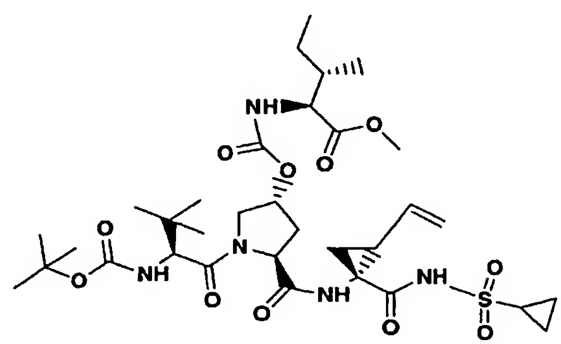
Compound 11

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(4-methoxy-benzyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(89%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.18 (d, J=8.2 Hz, 2 H), 6.85 (d, J=8.6 Hz, 2 H), 5.76 (m, 1 H), 5.31 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.34 (m, 1 H), 4.25 (t, J=9.5 Hz, 1 H), 4.19 (m, 2 H), 4.05 (m, 1 H), 3.92 (m, 1 H), 3.75 (s, 3 H), 2.92 (m, 1 H), 2.32 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.22 (q, J=8.5 Hz, 1 H), 2.13 (m, 1 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.43 (s, 9 H), 1.36 (m, 1 H), 1.22 (m, 2 H), 1.05 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.55 ; MS m/z 720 (M+H).



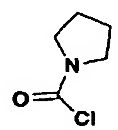
Reagent employed for preparation of Compound 12

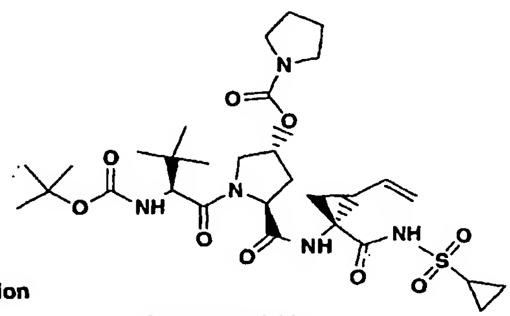


Compound 12

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-[(2S,3S)-3-methylvaleric acid methyl ester])))-P1(*1R*,*2S* VinylAcca)-CONHSO$_2$Cyclo propane

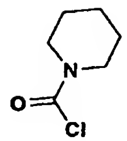
(68%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 6.63 (d, J=9.2 Hz, 1 H), 5.77 (m, 1 H), 5.30 (m, 2 H), 5.12 (d, J=10.4 Hz, 1 H), 4.35 (m, 1 H), 4.27 (d, J=9.2 Hz, 1 H), 4.12 (d, J=5.8 Hz, 1 H), 4.02 (m, 1 H), 3.96 (m, 1 H), 3.70 (s, 3 H), 2.92 (m, 1 H), 2.33 (dd, J=13.7 Hz, 7.0 Hz, 1 H), 2.24 (m, 1 H), 2.13 (m, 1 H), 1.86 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.80 (m, 1 H), 1.45 (s, 11 H), 1.24 (m, 3 H), 1.06 (m, 2 H), 1.01 (s, 9 H), 0.90 (m, 6 H). LC-MS A (retention time: 2.63 ; MS m/z 728 (M+H).


Reagent employed for preparation of Compound 13

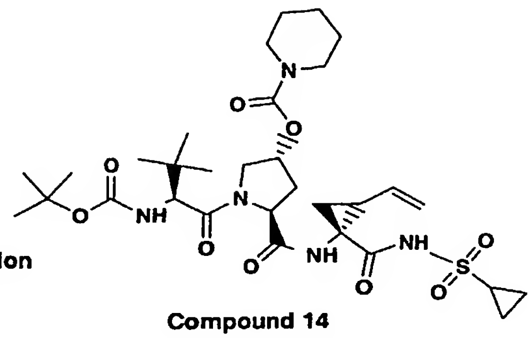

Compound 13

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-(pyrrolidino))))-P1(*1R*,*2S* VinylAcca)-CONHSO$_2$Cyclopropane

(57%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 6.60 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.30 (m, 2 H), 5.12 (d, J=10.4 Hz, 1 H), 4.37 (dd, J=10.1 Hz, 7.3 Hz, 1 H), 4.22 (d, J=9.5 Hz, 1 H), 4.16 (d, J=11.6 Hz, 1 H), 3.90 (dd, J=11.9 Hz, 3.4 Hz, 1 H), 3.34 (s, 4 H), 2.93 (m, 1 H), 2.34 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.22 (q, J=8.9 Hz, 1 H), 2.13 (m, 1 H), 1.86 (m, 5 H), 1.43 (s, 10 H), 1.23 (t, J=7.0 Hz, 2 H), 1.05 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.40 ; MS m/z 654 (M+H).



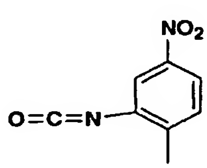
Reagent employed for preparation of Compound 14



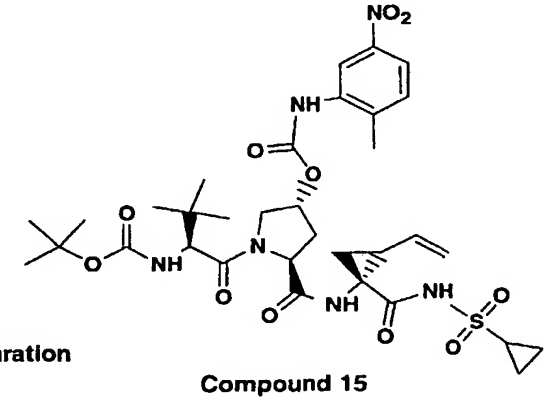
Compound 14

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-(piperdino))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(77%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 6.61 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.28 (s, 1 H), 5.12 (d, J=10.1 Hz, 1 H), 4.35 (dd, J=10.3 Hz, 7.3 Hz, 1 H), 4.22 (d, J=9.5 Hz, 1 H), 4.14 (d, J=11.6 Hz, 1 H), 3.91 (dd, J=11.6 Hz, 3.4 Hz, 1 H), 3.40 (s, 4 H), 2.93 (m, 1 H), 2.34 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.21 (q, J=8.8 Hz, 1 H), 2.13 (m, 1 H), 1.86 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.60 (m, 2 H), 1.51 (m, 4 H), 1.43 (s, 10 H), 1.23 (t, J=7.0 Hz, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.55 ; MS m/z 668 (M+H).



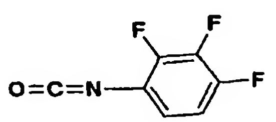
Reagent employed for preparation of Compound 15



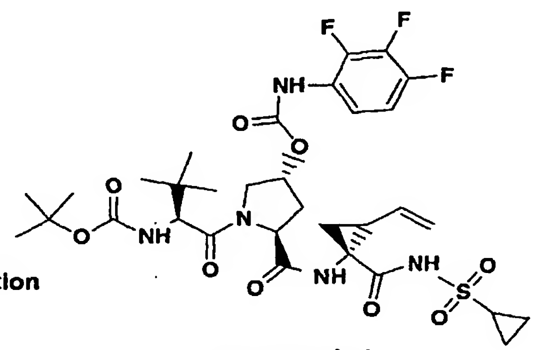
Compound 15

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-methyl-5-nitro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(75%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.53 (s, 1 H), 7.89 (d, J=10.1 Hz, 1 H), 7.40 (d, J=8.6 Hz, 1 H), 6.63 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.44 (s, 1 H), 5.29 (d, J=17.4 Hz, 1 H), 5.11 (d, J=10.7 Hz, 1 H), 4.44 (m, 1 H), 4.29 (d, J=9.5 Hz, 1 H), 4.25 (d, J=11.3 Hz, 1 H), 4.00 (dd, J=11.6 Hz, 3.4 Hz, 1 H), 2.92 (m, 1 H), 2.47 (m, 1 H), 2.34 (s, 3 H), 2.22 (m, 2 H), 1.87 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.43 (m, 1 H), 1.38 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.07 (m, 2 H), 1.03 (s, 9 H). LC-MS A (retention time: 2.61 ; MS m/z 735 (M+H).



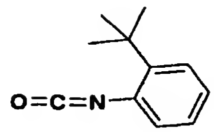
Reagent employed for preparation of Compound 16



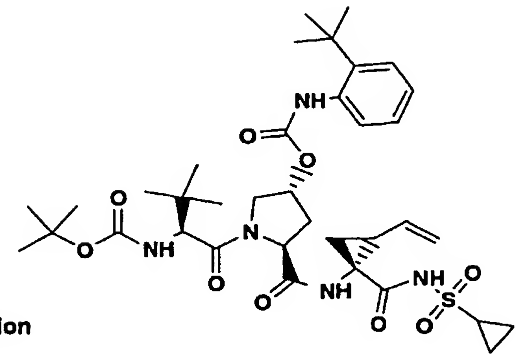
Compound 16

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,3,4-trifluoro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(49%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.63 (s, 1 H), 7.07 (q, J=9.8 Hz, 1 H), 6.65 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.42 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=11.6 Hz, 1 H), 4.40 (s, 1 H), 4.26 (d, J=9.5 Hz, 1 H), 4.21 (d, J=11.9 Hz, 1 H), 3.96 (dd, J=11.9 Hz, 3.9 Hz, 1 H), 2.93 (m, 1 H), 2.42 (dd, J=14.0 Hz, 6.7 Hz, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.43 (m, 1 H), 1.39 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.69 ; MS m/z 730 (M+H).



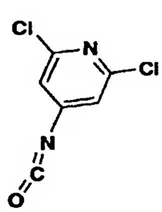
Reagent employed for preparation of Compound 17



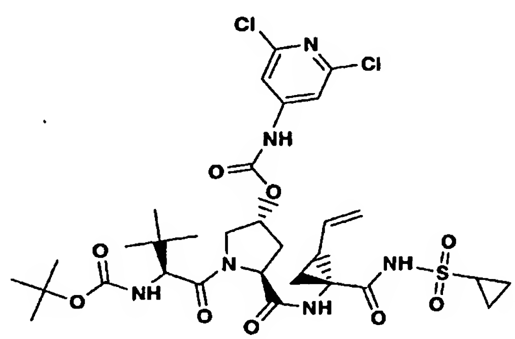
Compound 17

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-tert-butyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(52%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.42 (d, J=7.6 Hz, 1 H), 7.20 (m, 3 H), 6.65 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.37 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.44 (s, 1 H), 4.30 (d, J=9.2 Hz, 1 H), 4.16 (m, 1 H), 3.97 (m, 1 H), 2.92 (m, 1 H), 2.39 (m, 1 H), 2.22 (m, 2 H), 1.86 (m, 1 H), 1.50 (m, 1 H), 1.45 (s, 9 H), 1.37 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.75 ; MS m/z 732 (M+H).



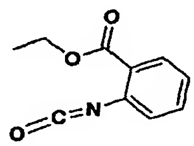
Reagent employed for preparation of Compound 18



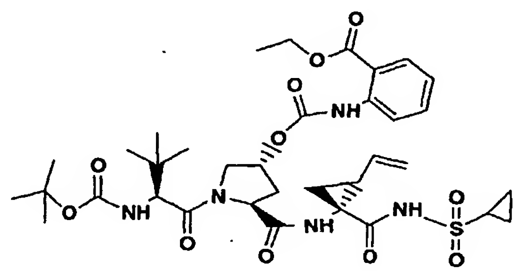
Compound 18

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,6-Dichloro-pyridin-4-yl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(20%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.47 (s, 2 H), 5.83 (m, 1 H), 5.40 (s, 1 H), 5.25 (d, J=17.1 Hz, 1 H), 5.08 (d, J=9.8 Hz, 1 H), 4.43 (m, 1 H), 4.30 (d, J=11.6 Hz, 1 H), 4.21 (m, 1 H), 3.96 (dd, J=12.2 Hz, 3.1 Hz, 1 H), 2.81 (m, 1 H), 2.44 (m, 1 H), 2.39 (m, 1 H), 2.17 (m, 2 H), 1.85 (m, 1 H), 1.37 (m, 1 H), 1.33 (s, 9 H), 1.16 (m, 2 H), 1.01 (s, 9 H), 0.98 (m, 2 H). LC-MS A (retention time: 2.73 ; MS m/z 768 (M+Na).



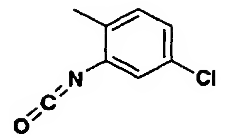
Reagent employed for preparation of Compound 19



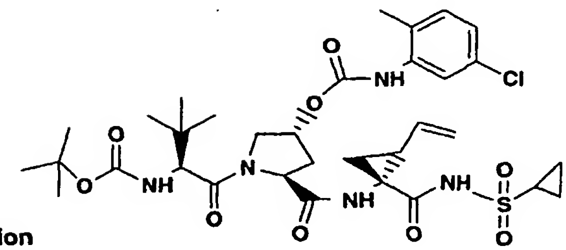
Compound 19

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid ethyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(50%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 8.36 (d, J=8.2 Hz, 1 H), 8.01 (d, J=7.0 Hz, 1 H), 7.54 (t, J=7.3 Hz, 1 H), 7.07 (t, J=7.3 Hz, 1 H), 5.85 (m, 1 H), 5.39 (s, 1 H), 5.24 (d, J=17.1 Hz, 1 H), 5.06 (d, J=10.1 Hz, 1 H), 4.47 (t, J=8.5 Hz, 1 H), 4.34 (m, 4 H), 4.23 (s, 1 H), 3.98 (d, J=9.2 Hz, 1 H), 2.83 (m, 1 H), 2.47 (m, 1 H), 2.29 (m, 1 H), 2.16 (m, 1 H), 1.85 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.38 (t, J=7.0 Hz, 3 H), 1.32 (m, 1 H), 1.28 (s, 9 H), 1.15 (s, 2 H), 1.03 (s, 9 H), 0.99 (m, 2 H). LC-MS F (retention time: 3.48 ; MS m/z 747 (M+H).



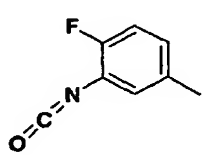
Reagent employed for preparation of Compound 20



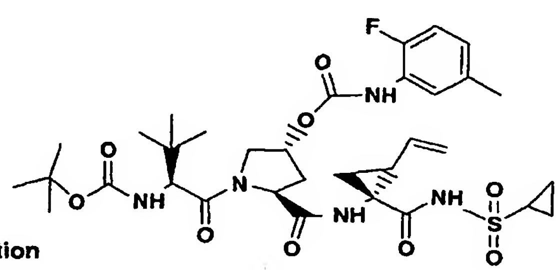
Compound 20

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-chloro-2-methyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(40%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.60 (s, 1 H), 7.14 (d, J=7.9 Hz, 1 H), 7.03 (d, J=8.2 Hz, 1 H), 5.87 (m, 1 H), 5.37 (s, 1 H), 5.24 (d, J=17.1 Hz, 1 H), 5.05 (d, J=9.8 Hz, 1 H), 4.45 (m, 1 H), 4.26 (s, 1 H), 4.22 (d, J=11.9 Hz, 1 H), 3.98 (m, 1 H), 2.81 (m, 1 H), 2.44 (m, 1 H), 2.30 (m, 1 H), 2.20 (s, 3 H), 2.16 (m, 1 H), 1.84 (dd, J=7.6 Hz, 5.2 Hz, 1 H), 1.39 (s, 10 H), 1.13 (s, 2 H), 1.03 (s, 9 H), 0.96 (s, 2 H). LC-MS A (retention time: 2.76 ; MS m/z 724 (M+H).



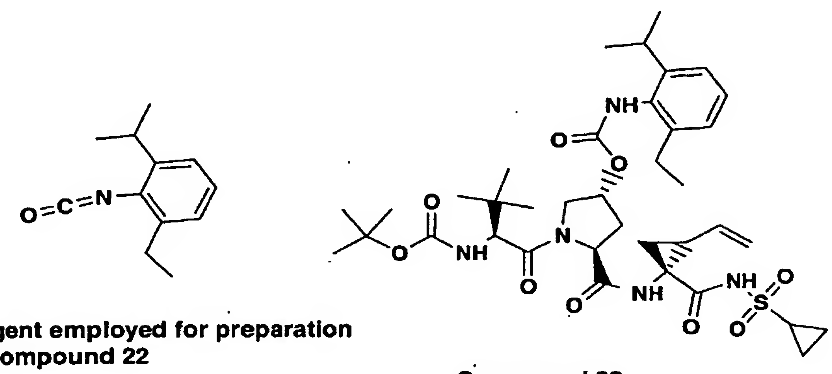
Reagent employed for preparation of Compound 21



Compound 21

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-fluoro-5-methyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(53%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.69 (s, 1 H), 6.96 (t, J=8.2 Hz, 1 H), 6.86 (s, 1 H), 5.85 (m, 1 H), 5.38 (s, 1 H), 5.23 (d, J=17.4 Hz, 1 H), 5.06 (d, J=10.1 Hz, 1 H), 4.45 (m, 1 H), 4.25 (s, 1 H), 4.22 (d, J=11.9 Hz, 1 H), 3.98 (m, 1 H), 2.81 (m, 1 H), 2.44 (m, 1 H), 2.28 (s, 4 H), 2.14 (m, 1 H), 1.85 (m, 1 H), 1.37 (s, 10 H), 1.14 (s, 2 H), 1.03 (s, 9 H), 0.96 (s, 2 H). LC-MS A (retention time: 2.69 ; MS m/z 708 (M+H).

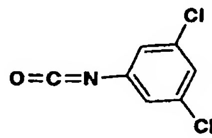


Reagent employed for preparation of Compound 22

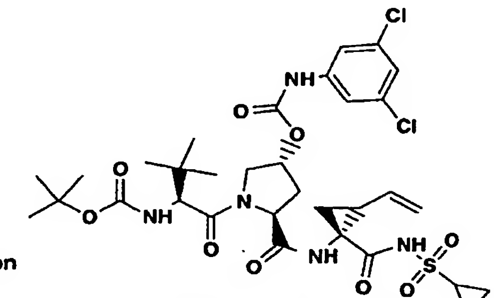
Compound 22

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-ethyl-6-isopropyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

BMS-557166 (78%): ^{1}H NMR (d_6-DMSO, 500Mz) δ 10.40 (s,1 H), 7.22 (t, J=7.6 Hz, 1 H), 7.15 (d, J=7.6 Hz, 1 H), 7.08 (d, J=7.3 Hz, 1 H), 6.38 (d, J=8.5 Hz, 1 H), 5.63 (m, 1 H), 5.34 (s, 1 H), 5.27 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.7 Hz, 1 H), 4.34 (m, 1 H), 4.14 (d, J=8.9 Hz, 1 H), 3.96 (m, 1 H), 3.85 (d, J=11.9 Hz, 1 H), 3.09 (m, 1 H), 2.93 (m, 1 H), 2.50 (m, 2 H), 2.22 (m, 2 H), 2.13 (m, 1 H), 1.72 (m, 1 H), 1.41 (s, 10 H), 1.21 (m, 9 H), 1.03 (m, 2 H), 0.96 (s, 9 H), 0.90 (s, 2 H). LC-MS A (retention time: 2.81 ; MS m/z 746 (M+H).



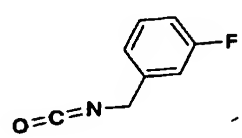
Reagent employed for preparation of Compound 23



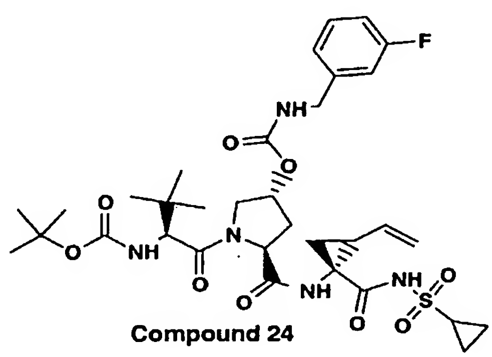
Compound 23

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3,5-dichloro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(64%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.44 (s, 2 H), 7.04 (s, 1 H), 6.62 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.40 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.40 (dd, J=10.1 Hz, 7.3 Hz, 1 H), 4.25 (m, 2 H), 3.96 (dd, J=11.9 Hz, 3.6 Hz, 1 H), 2.92 (m, 1 H), 2.42 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.23 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (m, 1 H), 1.35 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.05 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.96 ; MS m/z 745 (M+H).



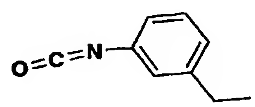
Reagent employed for preparation of Compound 24



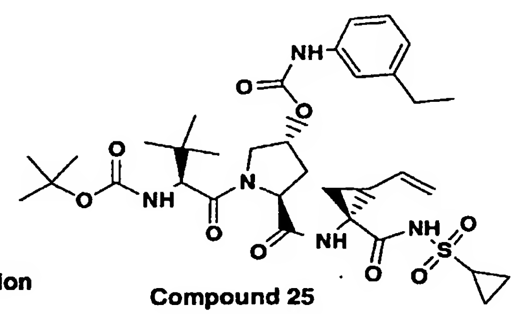
Compound 24

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-fluoro-benzyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(57%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.32 (m, 1 H), 7.08 (d, J=7.6 Hz, 1 H), 7.01 (d, J=10.1 Hz, 1 H), 6.96 (t, J=8.2 Hz, 1 H), 6.63 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.33 (s, 1 H), 5.30 (d, J=18.6 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.35 (m, 1 H), 4.25 (m, 3 H), 4.05 (m, 1 H), 3.95 (m, 1 H), 2.92 (m, 1 H), 2.33 (dd, J=13.4 Hz, 7.0 Hz, 1 H), 2.22 (m, 1 H), 2.13 (m, 1 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.43 (s, 9 H), 1.38 (m, 1 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.80 ; MS m/z 708 (M+H).



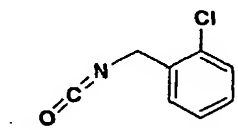
Reagent employed for preparation of Compound 25



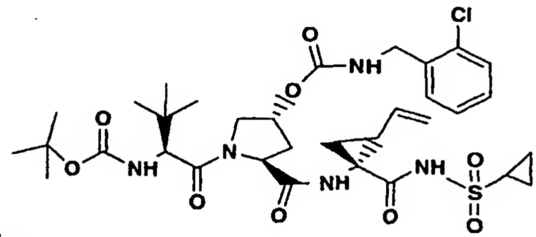
Compound 25

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-ethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(77%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.27 (s, 1 H), 7.21 (s, 1 H), 7.15 (t, J=7.6 Hz, 1 H), 6.86 (d, J=7.0 Hz, 1 H), 6.64 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.39 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.40 (dd, J=9.7 Hz, 7.3 Hz, 1 H), 4.28 (d, J=9.2 Hz, 1 H), 4.18 (d, J=11.6 Hz, 1 H), 3.97 (M, 1 H), 2.93 (M, 1 H), 2.59 (q, J=7.6 Hz, 2 H), 2.41 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (m, 1 H), 1.38 (s, 9 H), 1.23 (m, 2 H), 1.20 (t, J=7.3 Hz, 3 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.78 ; MS m/z 704 (M+H).



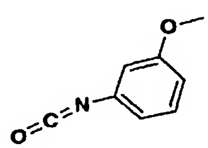
Reagent employed for preparation of Compound 26



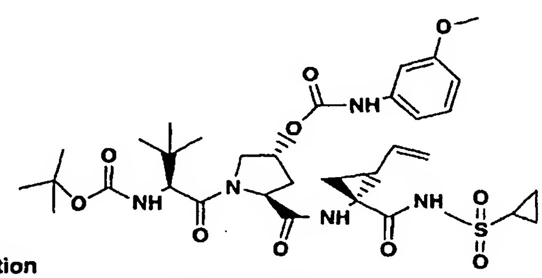
Compound 26

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-chloro-benzyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(62%): ^{1}H NMR (d_6-acetone, 500Mz) δ 8.39 (s, 1 H), 7.41 (m, 2 H), 7.32 (m, 2 H), 6.96 (s, 1 H), 5.80 (m, 2 H), 5.36 (s, 1 H), 5.23 (d, J=17.1 Hz, 1 H), 5.06 (d, J=10.7 Hz, 1 H), 4.42 (m, 2 H), 4.29 (d, J=9.5 Hz, 1 H), 3.99 (s, 1 H), 2.92 (m, 1 H), 2.33 (m, 1 H), 2.23 (m, 2 H), 1.79 (dd, J=7.6 Hz, 5.5 Hz, 1 H), 1.46 (m, 1 H), 1.42 (s, 9 H), 1.16 (m, 2 H), 1.04 (s, 11 H). LC-MS A (retention time: 2.58 ; MS m/z 724 (M+H).



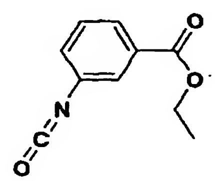
Reagent employed for preparation of Compound 27



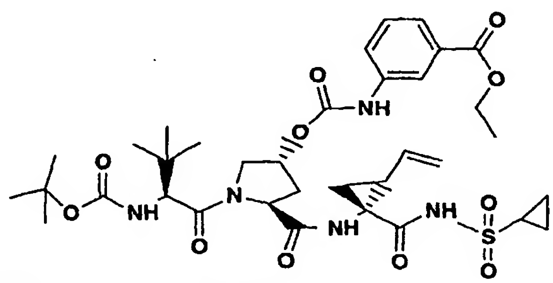
Compound 27

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-methoxy-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(47%): ^{1}H NMR (d_6-acetone, 500Mz) δ 10.11 (s, 1 H), 8.72 (s, 1 H), 8.40 (s, 1 H), 7.26 (s, 1 H), 7.19 (t, J=8.2 Hz, 1 H), 7.10 (d, J=7.6 Hz, 1 H), 6.61 (d, J=8.2 Hz, 1 H), 5.77 (m, 2 H), 5.47 (s, 1 H), 5.24 (d, J=17.4 Hz, 1 H), 5.08 (d, J=10.4 Hz, 1 H), 4.37 (m, 1 H), 4.30 (d, J=9.5 Hz, 1 H), 4.06 (m, 2 H), 3.77 (s, 3 H), 2.94 (m, 1 H), 2.40 (m, 1 H), 2.26 (m, 2 H), 1.80 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.50 (m, 1 H), 1.37 (s, 9 H), 1.20 (t, J=7.0 Hz, 2 H), 1.07 (m, 2 H), 1.05 (s, 9 H). LC-MS A (retention time: 2.51 ; MS m/z 706 (M+H).



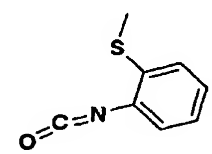
Reagent employed for preparation of Compound 28



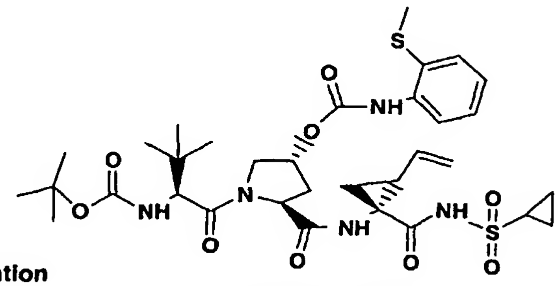
Compound 28

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-benzoic acid ethyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(43%): ^{1}H NMR (d_6-acetone, 500Mz) δ 10.10 (s, 1 H), 9.01 (s, 1 H), 8.40 (s, 1 H), 8.26 (s, 1 H), 7.79 (d, J=7.0 Hz, 1 H), 7.69 (d, J=7.6 Hz, 1 H), 7.44 (t, J=7.9 Hz, 1 H), 5.77 (m, 2 H), 5.49 (s, 1 H), 5.23 (d, J=17.4 Hz, 1 H), 5.08 (d, J=10.1 Hz, 1 H), 4.41 (t, J=7.6 Hz, 1 H), 4.35 (q, J=7.0 Hz, 2 H), 4.29 (d, J=9.5 Hz, 1 H), 4.16 (d. J=11.6 Hz, 1 H), 4.03 (m, 1 H), 2.94 (m, 1 H), 2.42 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.26 (m, 2 H), 1.80 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.50 (dd, J=9.5 Hz, 5.5 Hz, 1 H), 1.35 (m, 12 H), 1.20 (t, J=7.0 Hz, 2 H), 1.07 (m, 2 H), 1.04 (s, 9 H). LC-MS A (retention time: 2.63 ; MS m/z 748 (M+H).



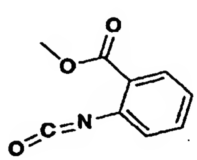
Reagent employed for preparation of Compound 29



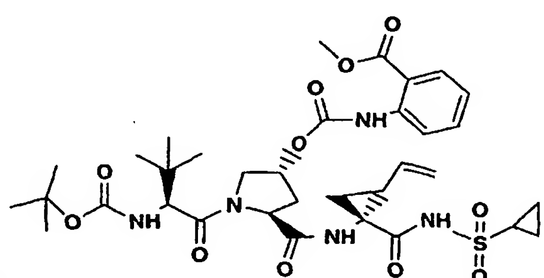
Compound 29

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-methylsulfanyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-$CONHSO_2$Cyclopropane

(63%): ^{1}H NMR (d_6-acetone, 500Mz) δ 10.13 (s, 1 H), 8.40 (s, 1 H), 7.99 (s, 1 H), 7.90 (s, 1 H), 7.46 (d, J=7.6 Hz, 1 H), 7.27 (t, J=7.6 Hz, 1 H), 7.12 (t, J=7.6 Hz, 1 H), 5.79 (m, 2 H), 5.46 (s, 1 H), 5.25 (d, J=17.1 Hz, 1 H), 5.08 (d, J=10.4 Hz, 1 H), 4.43 (m, 1 H), 4.28 (d, J=9.5 Hz, 1 H), 4.20 (d, J=11.3 Hz, 1 H), 4.03 (m, 1 H), 2.95 (m, 1 H), 2.44 (m, 1 H), 2.40 (s, 3 H), 2.27 (m, 2 H), 1.80 (dd. J=7.9 Hz, 5.2 Hz, 1 H), 1.50 (dd, J=9.5 Hz, 5.2 Hz, 1 H), 1.36 (s, 9 H), 1.20 (t, J=7.3 Hz, 2 H), 1.05 (s, 11 H). LC-MS A (retention time: 2.57 ; MS m/z 722 (M+H).



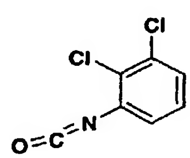
Reagent employed for preparation of Compound 30



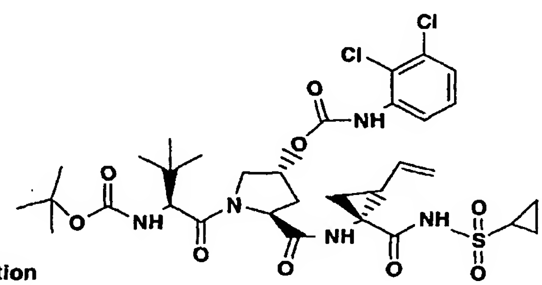
Compound 30

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid methyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(18%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.37 (d, J=8.2 Hz, 1 H), 8.01 (d, J=6.7 Hz, 1 H), 7.55 (t, J=8.6 Hz, 1 H), 7.08 (t, J=7.3 Hz, 1 H), 5.81 (m, 1 H), 5.39 (s, 1 H), 5.25 (d, J=17.1 Hz, 1 H), 5.07 (d, J=10.4 Hz, 1 H), 4.46 (m, 1 H), 4.32 (d, J=12.2 Hz, 1 H), 4.23 (s, 1 H), 3.98(d, J=12.2 Hz, 1 H), 3.89 (s, 3 H), 2.87 (m, 1 H), 2.46 (m, 1 H), 2.29 (m, 1 H), 2.15 (s, 1 H), 1.85 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.38 (m, 1 H), 1.28 (s, 9 H), 1.15 (s, 2 H), 1.03 (s, 11 H). LC-MS A (retention time: 2.75 ; MS m/z 734 (M+H).



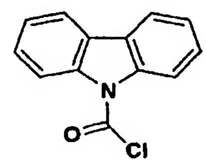
Reagent employed for preparation of Compound 31



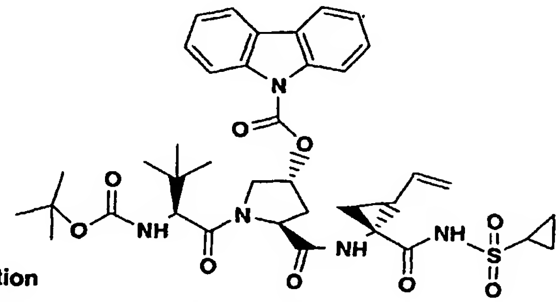
Compound 31

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,3-dichloro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(30%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.81 (s, 1 H), 7.27 (m, 2 H), 6.62 (d, J=9.2 Hz, 1 H), 5.78 (m, 1 H), 5.41 (s, 1 H), 5.27 (d, J=17.4 Hz, 1 H), 5.09 (d, J=10.6 Hz, 1 H), 4.42 (m, 1 H), 4.25 (m, 2 H), 3.97 (m, 1 H), 2.91 (m, 1 H), 2.43 (dd, J=13.4 Hz, 6.7 Hz, 1 H), 2.20 (m, 2 H), 1.85 (dd, J=7.9 Hz, 5.2 Hz, 1 H), 1.40 (m, 1 H), 1.37 (s, 9 H), 1.19 (m, 2 H), 1.01 (s, 11 H). LC-MS A (retention time: 2.78 ; MS m/z 744 (M+H).



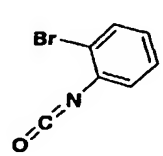
Reagent employed for preparation of Compound 32



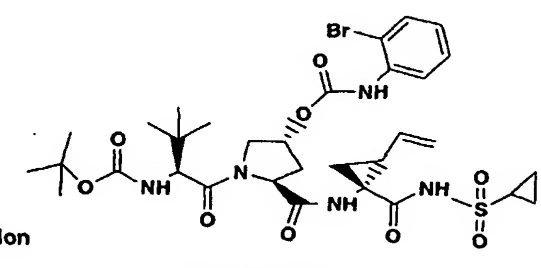
Compound 32

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N-(9-carbazolyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(27%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 8.18 (s, 2 H), 8.03 (d, J=7.6 Hz, 2 H), 7.48 (t, J=8.5 Hz, 2 H), 7.37 (t, J=7.3 Hz, 2 H), 5.80 (s, 1 H), 5.75 (m, 1 H), 5.29 (d, J=17.4, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.63 (m, 2 H), 4.30 (m, 1 H), 4.07 (m, 1 H), 2.94 (m, 1 H), 2.68 (m, 1 H), 2.35 (m, 1 H), 2.24 (m, 1 H), 1.89 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.44 (m, 1 H), 1.23 (m, 2 H), 1.08 (m, 2 H), 1.05 (s, 9 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.96 ; MS m/z 750 (M+H).



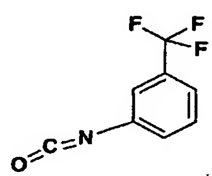
Reagent employed for preparation of Compound 33



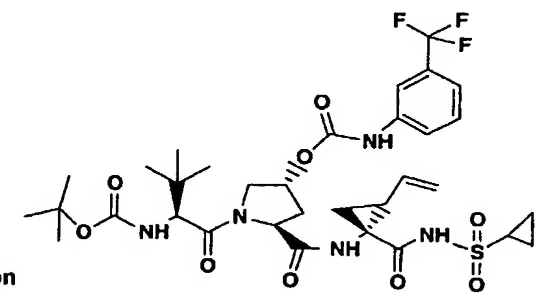
Compound 33

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-bromo-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(35%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.75 (m, 1 H), 7.57 (d, J=9.2 Hz, 1 H), 7.32 (t, J=8.5 Hz, 1 H), 7.05 (t, J=7.9 Hz, 1 H), 6.65 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.41 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.40 (m, 1 H), 4.27 (d, J=9.5 Hz, 1 H), 4.23 (d, J=11.9 Hz, 1 H), 3.97 (dd, J=11.9 Hz, 3.4 Hz, 1 H), 2.93 (m, 1 H), 2.41 (m, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.43 (m, 1 H), 1.39 (s, 9 H), 1.23 (t, J=7.3 Hz, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.65 ; MS m/z 754 (M+H).



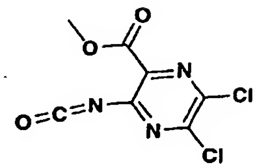
Reagent employed for preparation of Compound 34



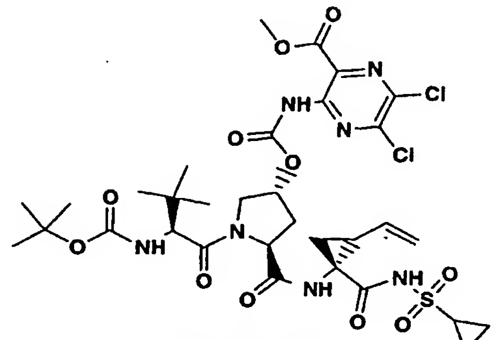
Compound 34

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-trifluoromethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(29%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.84 (s, 1 H), 7.60 (d, J=7.0 Hz, 1 H), 7.44 (m, 1 H), 7.29 (d, J=7.3 Hz, 1 H), 6.63 (d, J=9.2 Hz, 1 H), 5.78 (m, 1 H), 5.41 (s, 1 H), 5.28 (d, J=17.4 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.42 (m, 1 H), 4.25 (m, 2 H), 3.96 (dd, J=11.9 Hz, 3.4 Hz, 1 H), 2.91 (m, 1 H), 2.43 (dd, J=13.7 Hz, 7.0 Hz, 1 H), 2.21 (m, 2 H), 1.86 (dd, J=8.2 Hz, 5.2 Hz, 1 H), 1.42 (m, 1 H), 1.34 (s, 9 H), 1.22 (m, 2 H), 1.02 (s, 9 H), 1.02 (m, 2 H). LC-MS A (retention time: 2.79 ; MS m/z 743 (M+H).



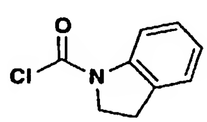
Reagent employed for preparation of Compound 35



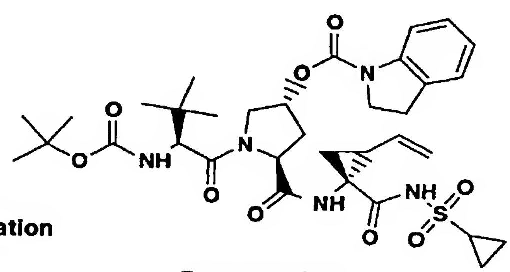
Compound 35

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-3-(5,6-Dichloro-pyrazine-2-carboxylic acid methyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(48%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 6.64 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.45 (s, 1 H), 5.30 (d, J=17.4 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.42 (dd, J=10.3 Hz, 7.0 Hz, 1 H), 4.23 (m, 2 H), 3.99 (dd, J=11.6 Hz, 3.6 Hz, 1 H), 3.95 (s, 3 H), 2.93 (m, 1 H), 2.44 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.24 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.41 (m, 1 H), 1.37 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.67 ; MS m/z 804 (M+H).



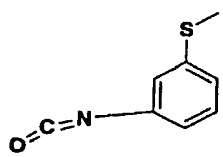
Reagent employed for preparation of Compound 36



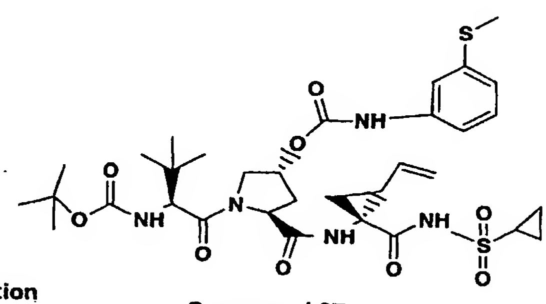
Compound 36

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N-(1-indolinyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(78%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.76 (s, 1 H), 7.51 (m, 2 H), 6.94 (m, 1 H), 6.59 (m, 1 H), 5.75 (m, 1 H), 5.41 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.12 (d, J=11.3 Hz, 1 H), 4.44 (s, 1 H), 4.28 (s, 1 H), 4.21 (s, 1 H), 3.96 (m, 3 H), 3.07 (s, 2 H), 2.93 (m, 1 H), 2.46 (s, 1 H), 2.21 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (m, 1 H), 1.31 (s, 9 H), 1.22 (m, 2 H), 1.06 (m, 2 H), 1.03 (s, 9 H). LC-MS A (retention time: 2.68 ; MS m/z 702 (M+H).



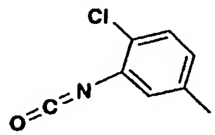
Reagent employed for preparation of Compound 37



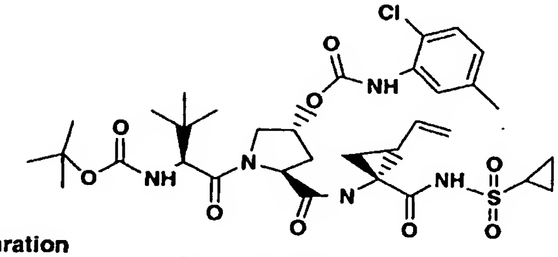
Compound 37

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-methylsulfanyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(17%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.41 (s, 1 H), 7.15 (m, 2 H), 6.91 (d, J=7.0 Hz, 1 H), 5.77 (m, 1 H), 5.38 (s, 1 H), 5.28 (d, J=16.8 Hz, 1 H), 5.10 (d, J=9.5 Hz, 1 H), 4.41 (m, 1 H), 4.26 (m, 1 H), 4.20 (d, J=11.9 Hz, 1 H), 3.96 (dd, J=11.6 Hz, 3.6 Hz, 1 H), 2.69 (m, 1 H), 2.44 (s, 3 H), 2.40 (m, 1 H), 2.20 (s, 2 H), 1.86 (m, 1 H), 1.41 (m, 1 H), 1.37 (s, 9 H), 1.20 (s, 2 H), 1.02 (s, 11 H). LC-MS A (retention time: 2.69 ; MS m/z 622 (M+H-Boc).



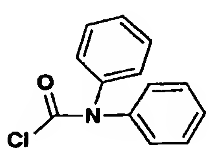
Reagent employed for preparation of Compound 38



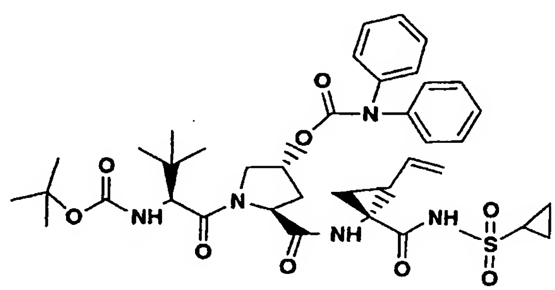
Compound 38

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-chloro-5-methyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(27%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.64 (s, 1 H), 7.25 (d, J=8.2 Hz, 1 H), 6.92 (d, J=7.9 Hz, 1 H), 6.59 (d, J=8.5 Hz, 1 H), 5.80 (m, 1 H), 5.39 (s, 1 H), 5.26 (d, J=17.4 Hz, 1 H), 5.07 (d, J=10.1 Hz, 1 H), 4.42 (m, 1 H), 4.26 (m, 2 H), 3.98 (d, J=11.6 Hz, 1 H), 2.89 (m, 1 H), 2.43 (m, 1 H), 2.31 (s, 3 H), 2.24 (m, 1 H), 2.15 (m, 1 H), 1.85 (dd, J=7.9 Hz, 5.2 Hz, 1 H), 1.39 (m, 1 H), 1.37 (s, 9 H), 1.17 (m, 2 H), 1.03 (s, 11 H). LC-MS A (retention time: 2.72 ; MS m/z 725 (M+H).



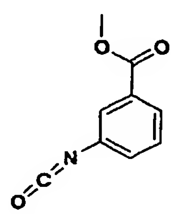
Reagent employed for preparation of Compound 39



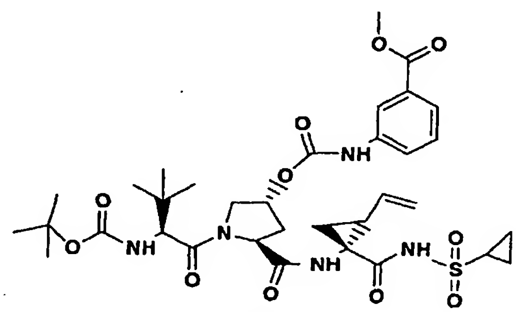
Compound 39

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-diphenyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(51%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.33 (m, 4 H), 7.22 (m, 6 H), 6.74 (d, J=9.2 Hz, 1 H), 5.72 (m, 1 H), 5.39 (s, 1 H), 5.27 (d, J=17.4 Hz, 1 H), 5.10 (d, J=10.4 Hz, 1 H), 4.29 (d, J=9.2 Hz, 1 H), 4.25 (d, J=11.9 Hz, 1 H), 4.05 (dd, J=10.3 Hz, 7.3 Hz, 1 H), 3.89 (dd, J=12.2 Hz, 3.0 Hz, 1 H), 2.92 (m, 1 H), 2.19 (m, 2 H), 2.08 (m, 1 H), 1.83 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.43 (s, 9 H), 1.36 (dd, J=9.5 Hz, 5.5 Hz, 1 H), 1.23 (t, J=7.0 Hz, 2 H), 1.05 (m, 2 H), 1.03 (s, 9 H). LC-MS A (retention time: 2.75 ; MS m/z 752 (M+H).



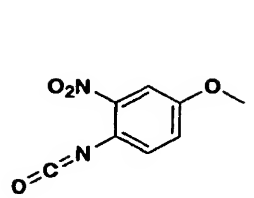
Reagent employed for preparation of Compound 40



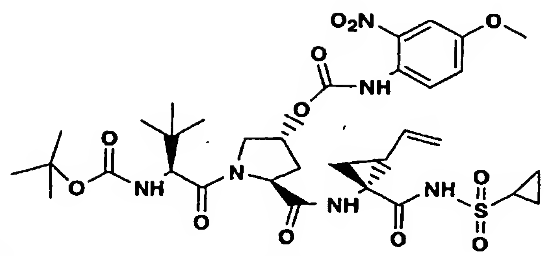
Compound 40

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-benzoic acid methyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(9%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.11 (s, 1 H), 7.66 (m, 2 H), 7.37 (t, J=7.9 Hz, 1 H), 6.60 (s, 1 H), 5.77 (s, 1 H), 5.41 (s, 1 H), 5.29 (d, J=16.8 Hz, 1 H), 5.11 (d, J=9.8 Hz, 1 H), 4.42 (m, 1 H), 4.26 (d, J=9.5 Hz, 1 H), 4.22 (d, J=12.5 Hz, 1 H), 3.96 (dd, J=11.6 Hz, 3.4 Hz, 1 H), 3.89 (s, 3 H), 2.90 (s, 1 H), 2.42 (m, 1 H), 2.21 (s, 2 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.41 (m, 1 H), 1.35 (s, 9 H), 1.22 (m, 2 H), 1.02 (s, 11 H). LC-MS A (retention time: 2.59 ; MS m/z 734 (M+H).



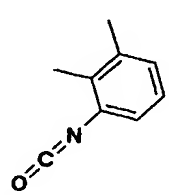
Reagent employed for preparation of Compound 41



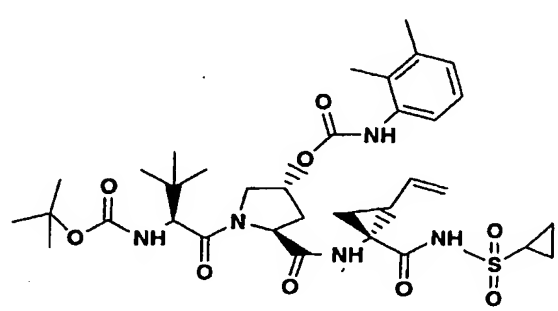
Compound 41

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(4-Methoxy-2-nitro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(23%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.05 (s, 1 H), 7.60 (d, J=3.1 Hz, 1 H), 7.28 (dd, J=9.2 Hz, 3.1 Hz, 1 H), 6.60 (d, J=8.6 Hz, 1 H), 5.76 (m, 1 H), 5.40 (s, 1 H), 5.28 (d, J=17.1 Hz, 1 H), 5.10 (d, J=10.4 Hz, 1 H), 4.42 (dd, J=10.1 Hz, 7.3 Hz, 1 H), 4.25 (m, 2 H), 3.97 (dd, J=11.9 Hz, 3.0 Hz, 1 H), 3.85 (s, 3 H), 2.92 (m, 1 H), 2.42 (dd, J=13.3 Hz, 7.0 Hz, 1 H), 2.21 (m, 2 H), 1.85 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.40 (m, 1 H), 1.34 (s, 9 H), 1.22 (m, 2 H), 1.02 (s, 11 H). LC-MS A (retention time: 2.63 ; MS m/z 773 (M+Na).



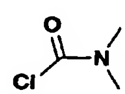
Reagent employed for preparation of Compound 42



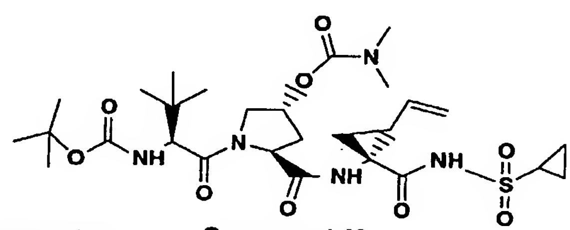
Compound 42

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,3-Dimethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(18%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.17 (m, 1 H), 7.00 (m, 2 H), 5.77 (m, 1 H), 5.38 (s, 1 H), 5.29 (d, J=16.8 Hz, 1 H), 5.11 (d, J=9.8 Hz, 1 H), 4.41 (s, 1 H), 4.29 (m, 1 H), 4.16 (d, J=11.6 Hz, 1 H), 3.97 (d, J=10.4 Hz, 1 H), 2.91 (s, 1 H), 2.41 (m, 1 H), 2.27 (s, 3 H), 2.21 (m, 2 H), 2.13 (s, 3 H), 1.86 (m, 1 H), 1.43 (s, 10 H), 1.22 (s, 2 H), 1.03 (s, 11 H). LC-MS A (retention time: 2.64 ; MS m/z 704 (M+H).



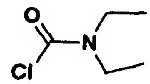
Reagent employed for preparation of Compound 43



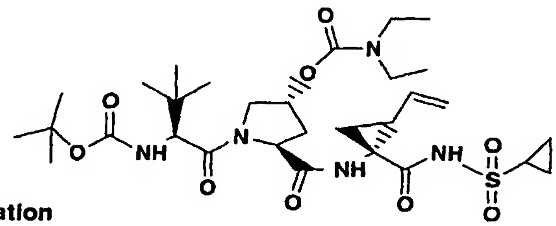
Compound 43

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-dimethyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(16%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 6.60 (d, J=8.9 Hz, 1 H), 5.76 (m 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.26 (s, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.38 (dd, J=10.0 Hz, 7.3 Hz, 1 H), 4.22 (m, 1 H), 4.16 (d, J=11.6 Hz, 1 H), 3.90 (dd, J=11.6 Hz, 3.1 Hz, 1 H), 2.92 (m, 1 H), 2,89 (s, 6 H), 2.35 (dd, J=14.0 Hz, 7.3 Hz, 1 H), 2.21 (m, 1 H), 2.16 (m, 1 H), 1.85 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (s, 10 H), 1.22 (m, 2 H), 1.05 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.28 ; MS m/z 628 (M+H).



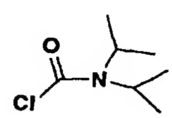
Reagent employed for preparation of Compound 44



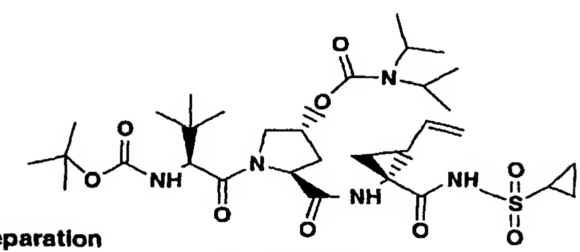
Compound 44

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-diethyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(27%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 6.59 (d, J=9.2 Hz, 1 H), 5.77 (m, 1 H), 5.29 (s, 1 H), 5.27 (d, J=16.5 Hz, 1 H), 5.10 (d, J=10.7 Hz, 1 H), 4.37 (dd, J=10.3 Hz, 7.3 Hz, 1 H), 4.23 (m, 1 H), 4.13 (d, J=12.5 Hz, 1 H), 3.90 (dd, J=11.3 Hz, 3.4 Hz, 1 H), 3.26 (m, 4 H), 2.91 (m, 1 H), 2.36 (dd, J=13.7 Hz, 7.0 Hz, 1 H), 2.18 (m, 2 H), 1.85 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.44 (m, 1 H), 1.42 (s, 9 H), 1.20 (m, 2 H), 1.10 (t, J=8.2 Hz, 6 H), 1.02 (s, 11 H). LC-MS A (retention time: 2.38 ; MS m/z 678 (M+Na).



Reagent employed for preparation of Compound 45

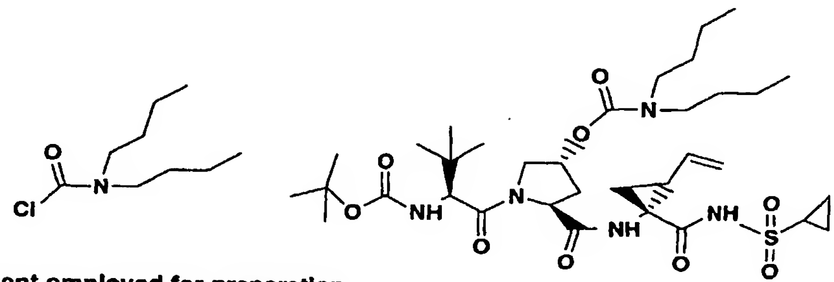


Compound 45

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-diisopropyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane.

(43%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 6.59 (d, J=9.5 Hz, 1 H), 5.76 (m, 1 H), 5.33 (s, 1 H), 5.30 (d, J=18.3 Hz, 1 H), 5.13 (d, J=10.4 Hz, 1 H), 4.41 (dd, J=10.7 Hz, 7.0 Hz, 1 H), 4.27 (m, 1 H), 4.14 (s, 1 H), 3.67 (s, 1 H), 4.10 (d, J=11.9 Hz, 1 H), 3.90 (dd, J=11.4 Hz, 3.4 Hz, 1 H), 2.93 (m, 1 H), 2.37 (dd, J=14.0 Hz, 7.0 Hz, 1 H), 2.24 (q, J=8.6 Hz, 1 H), 2.16 (m, 1 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.44 (m, 1 H),

1.42 (s, 9 H), 1.23 (m, 2 H), 1.19 (m, 12 H), 1.08 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.65 ; MS m/z 684 (M+H).

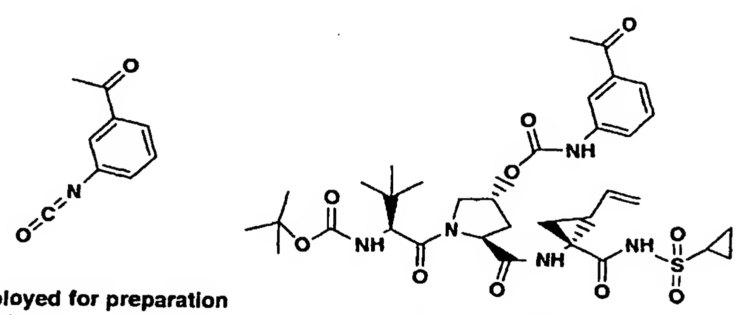


Reagent employed for preparation of Compound 46

Compound 46

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(N,N-dibutyl)))-P1(1*R*,2*S* VinylAcca)-$CONHSO_2$Cyclopropane

(39%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 5.83 (m, 1 H), 5.26 (s, 1 H), 5.24 (d, J=17.1 Hz, 1 H), 5.06 (d, J=10.4 Hz, 1 H), 4.41 (dd, J=9.8 Hz, 7.6 Hz, 1 H), 4.25 (m, 1 H), 4.09 (d, J=12.2 Hz, 1 H), 3.91 (dd, J=11.9 Hz, 3.3 Hz, 1 H), 3.20 (m, 4 H), 2.80 (m, 1 H), 2.38 (dd, J=13.7 Hz, 7.3 Hz, 1 H), 2.24 (m, 1 H), 2.15 (q, J=8.9 Hz, 1 H), 1.84 (dd, J=7.9 Hz, 5.2 Hz, 1 H), 1.53 (m, 2 H), 1.46 (m, 1 H), 1.43 (s, 9 H), 1.35 (m, 2 H), 1.30 (m, 4 H), 1.14 (s, 2 H), 1.02 (s, 9 H), 0.97 (m, 2 H), 0.92 (m, 6 H). LC-MS A (retention time: 2.78 ; MS m/z 713 (M+H).

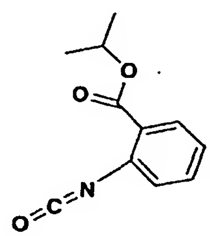


Reagent employed for preparation of Compound 47

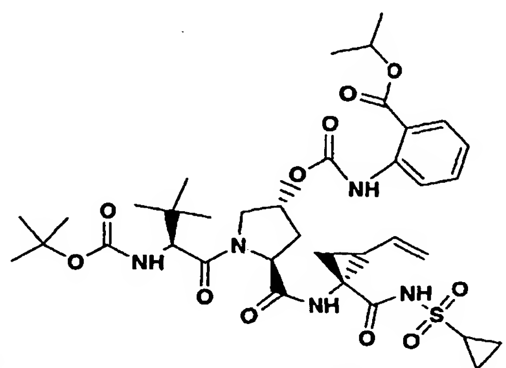
Compound 47

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-acetyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(54%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.05 (m, 1 H), 7.66 (m, 2 H), 7.40 (t, J=7.9 Hz, 1 H), 5.84 (s, 1 H), 5.39 (s, 1 H), 5.25 (d, J=15.3 Hz, 1 H), 5.07 (d, J=7.0 Hz, 1 H), 4.45 (t, J=7.9 Hz, 1 H), 4.26 (m, 1 H), 4.22 (d, J=12.5 Hz, 1 H), 3.97 (dd, J=11.9 Hz, 3.3 Hz, 1 H), 2.81 (brs, 1 H), 2.57 (s, 3 H), 2.44 (dd, J=13.7 Hz, 7.0 Hz, 1 H), 2.25 (s, 1 H), 2.16 (s, 1 H), 1.85 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.38 (m, 1 H), 1.34 (s, 9 H), 1.16 (m, 2 H), 1.01 (s, 11 H). LC-MS A (retention time: 2.48 ; MS m/z 718 (M+H).



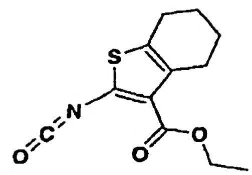
Reagent employed for preparation of Compound 48



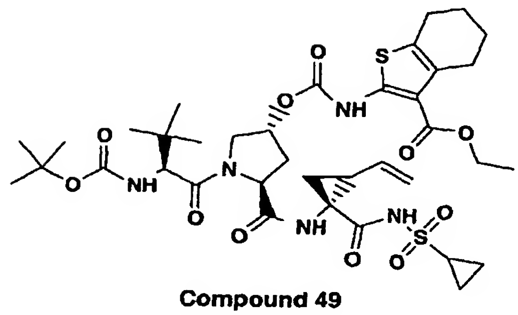
Compound 48

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid isopropyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(34%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.38 (d, J=8.2 Hz, 1 H), 8.00 (d, J=7.9 Hz, 1 H), 7.55 (t, J=8.2 Hz, 1 H), 7.06 (t, J=7.6 Hz, 1 H), 6.62 (d, J=9.5 Hz, 1 H), 5.76 (m, 1 H), 5.40 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.20 (m, 1 H), 5.12 (d, J=10.1 Hz, 1 H), 4.44 (m, 1 H), 4.32 (d, J=11.9 Hz, 1 H), 4.23 (m, 1 H), 3.96 (m, 1 H), 2.94 (m, 1 H), 2.45 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.23 (m, 2 H), 1.88 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.43 (dd, J=9.7 Hz, 5.5 Hz, 1 H), 1.37 (m, 6 H), 1.29 (s, 9 H), 1.23 (t. J=7.0 Hz, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS B (retention time: 2.56 ; MS m/z 763 (M+H).



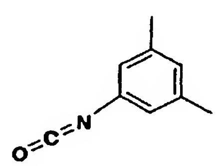
Reagent employed for preparation of Compound 49



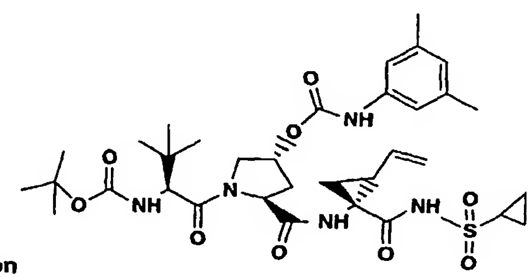
Compound 49

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-(4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylic acid ethyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(10%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 5.75 (m, 1 H), 5.42 (s, 1 H), 5.31 (dd, J=17.1 Hz, 5.5 Hz, 1 H), 5.13 (d, J=10.4 Hz, 1 H), 4.42 (m, 1 H), 4.32 (m, 1 H), 4.28 (m, 2 H), 4.20 (m, 1 H), 3.93 (m, 1 H), 2.93 (m, 1 H), 2.74 (s, 2 H), 2.62 (s, 2 H), 2.47 (m, 1 H), 2.25 (m, 2 H), 1.79 (m, 5 H), 1.38 (m, 1 H), 1.34 (m, 3 H), 1.31 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.02, 1.01 (s, total 9 H). LC-MS A (retention time: 3.08 ; MS m/z 809 (M+H).



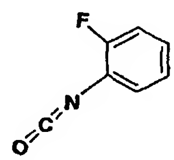
Reagent employed for preparation of Compound 50



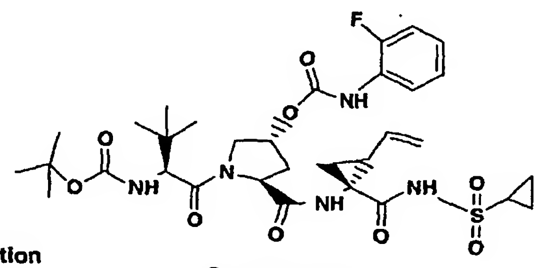
Compound 50

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3,5-dimethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(43%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.03 (m, 2 H), 6.67 (s, 1 H), 6.64 (d, J=9.2 Hz, 1 H), 5.77 (m, 1 H), 5.38 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.41 (m, 1 H), 4.27 (d, J=9.5 Hz, 1 H), 4.18 (d, J=11.9 Hz, 1 H), 3.97 (dd, J=11.9 Hz, 3.7 Hz, 1 H), 2.91 (m, 1 H), 2.41 (dd, J=13.7 Hz, 7.0 Hz, 1 H), 2.24 (s, 6 H), 2.21 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (m, 1 H), 1.38 (s, 9 H), 1.22 (m, 2 H), 1.05 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.73 ; MS m/z 704 (M+H).



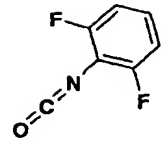
Reagent employed for preparation of Compound 51



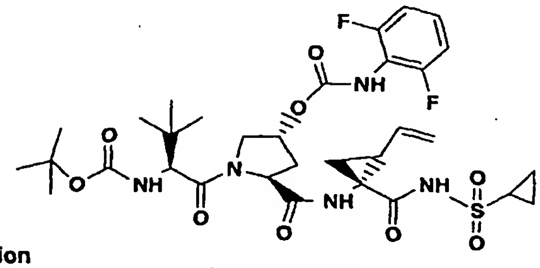
Compound 51

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-fluoro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(37%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.86 (s, 1 H), 7.10 (m, 3 H), 6.63 (d, J=8.9 Hz, 1 H), 5.77 (m, 1 H), 5.42 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.40 (m, 1 H), 4.27 (d, J=9.2 Hz, 1 H), 4.21 (d, J=11.9 Hz, 1 H), 3.96 (dd, J=11.9 Hz, 3.6 Hz, 1 H), 2.92 (m, 1 H), 2.42 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.42 (dd, J=9.5 Hz, 5.5 Hz, 1 H), 1.38 (s, 9 H), 1.23 (t, J=7.3 Hz, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.52 ; MS m/z 694 (M+H).



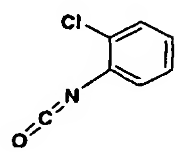
Reagent employed for preparation of Compound 52



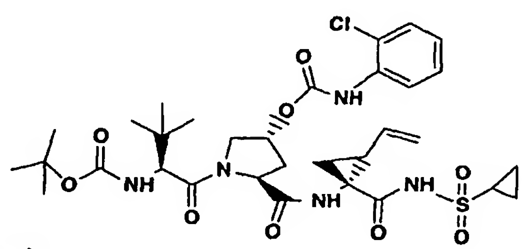
Compound 52

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,6-difluorophenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(34%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.28 (m, 1 H), 7.01 (t, J=7.9 Hz, 2 H), 6.65 (d, J=8.9 Hz, 1 H), 5.77 (m, 1 H), 5.41 (s, 1 H), 5.30 (d, J=17.4 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.36 (s, 1 H), 4.29 (d, J=9.5 Hz, 1 H), 4.10 (m, 1 H), 3.96 (d, J=8.9 Hz, 1 H), 2.92 (m, 1 H), 2.37 (s, 1 H), 2.21 (m, 2 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.44 (s, 10 H), 1.23 (t, J=7.0 Hz, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.38 ; MS m/z 712 (M+H).



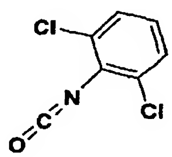
Reagent employed for preparation of Compound 53



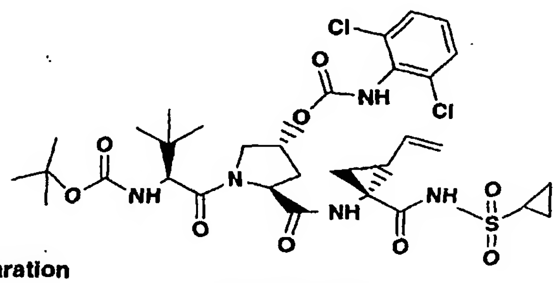
Compound 53

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-chloro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(37%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.81 (s, 1 H), 7.39 (d, J=7.9 Hz, 1 H), 7.28 (t, J=7.9 Hz, 1 H), 7.10 (t, J=7.6 Hz, 1 H), 6.64 (d, J=9.5 Hz, 1 H), 5.77 (m, 1 H), 5.42 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4Hz, 1 H), 4.41 (m, 1 H), 4.27 (d, J=9.5 Hz, 1 H), 4.23 (d, J=12.5 Hz, 1 H), 3.98 (dd, J=11.6 Hz, 3.1 Hz, 1 H), 2.92 (m, 1 H), 2.42 (dd, J=13.4 Hz, 6.7 Hz, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (dd, J=9.8 Hz, 5.5 Hz, 1 H), 1.38 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.59 ; MS m/z 711 (M+H).



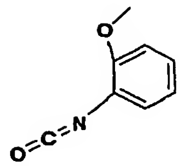
Reagent employed for preparation of Compound 54



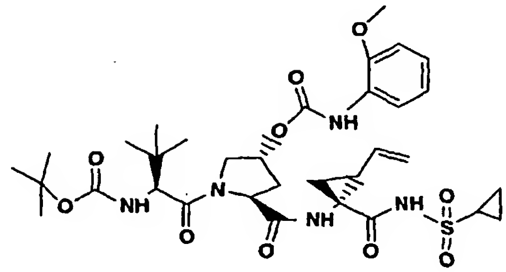
Compound 54

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,6-dichloro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(37%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.43 (d, J=7.9 Hz, 2 H), 7.27 (t, J=7.9 Hz, 1 H), 6.62 (s, 1 H), 5.77 (m, 1 H), 5.39 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.1 Hz, 1 H), 4.44 (s, 1 H), 4.29 (s, 1 H), 4.10 (m, 1 H), 4.10 (m, 1 H), 3.99 (m, 1 H), 2.92 (s, 1 H), 2.42 (s, 1 H), 2.22 (brs, 2 H), 1.86 (s, 1 H), 1.48 (s, 1 H), 1.45 (s, 9 H), 1.23 (t, J=7.3 Hz, 2 H), 1.06 (s, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.49 ; MS m/z 744 (M+H).



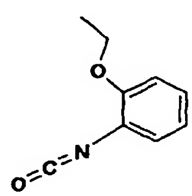
Reagent employed for preparation of Compound 55



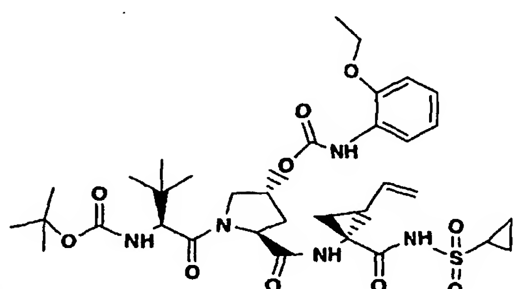
Compound 55

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-methoxy-phenyl))))-P1(*1R*,*2S* VinylAcca)-CONHSO$_2$Cyclopropane

(32%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.85 (s, 1 H), 7.03 (t, J=7.9 Hz, 1 H), 6.96 (d, J=7.9 Hz, 1 H), 6.90 (t, J=7.2 Hz, 1 H), 6.63 (d, J=8.9 Hz, 1 H), 5.77 (m, 1 H), 5.39 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=11.3 Hz, 1 H), 4.40 (t, J=9.6 Hz, 1 H), 4.26 (d, J=9.5 Hz, 1 H), 4.21 (d, J=12.2, 1 H), 3.97 (dd, J=11.6 Hz, 3.3 Hz, 1 H), 3,84 (s, 3 H), 2.92 (m, 1 H), 2.41 (m, 1 H), 2.23 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.42 (dd, J=9,5 Hz, 5.5 Hz, 1 H), 1.37 (s, 9 H), 1.23 (t, J=7.0 Hz, 2 H), 1.05 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.56 ; MS m/z 706 (M+H).



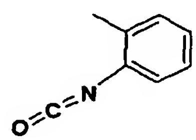
Reagent employed for preparation of Compound 56



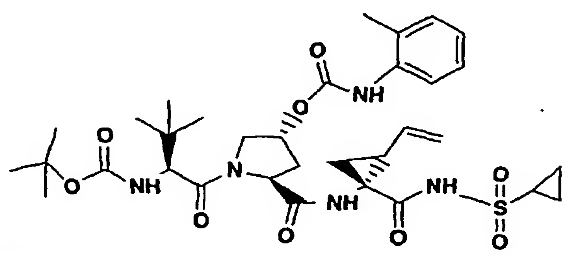
Compound 56

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-ethoxy-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(32%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.87 (s, 1 H), 7.00 (t, J=7.6 Hz, 1 H), 6.94 (d, J=7.9 Hz, 1 H), 6.88 (t, J=7.6 Hz, 1 H), 6.62 (d, J=8.9 Hz, 1 H), 5.79 (m, 1 H), 5.39 (s, 1 H), 5.27 (d, J=17.4 Hz, 1 H), 5.09 (d, J=10.4 Hz, 1 H), 4.42 (t, J=8.8 Hz, 1 H), 4.25 (t, J=9.8 Hz, 2 H), 4.08 (m, 2 H), 3.98 (d, J=8.8 Hz, 1 H), 2.91 (m, 1 H), 2.43 (dd, J=13.4Hz, 6.7 Hz, 1 H), 2.19 (m, 2 H), 1.85 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.41 (t, J=6.7 Hz, 4 H), 1.35 (s, 9 H), 1.19 (m, 2 H), 1.02 (s, 11 H). LC-MS A (retention time: 2.67 ; MS m/z 720 (M+H).



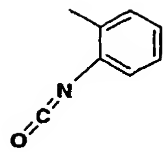
Reagent employed for preparation of Compound 57



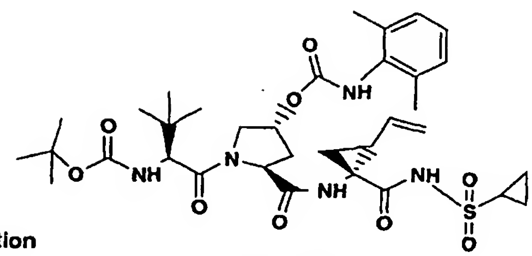
Compound 57

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(o-tolyl)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(40%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.37 (m, 1 H), 7.17 (t, J=7.6 Hz, 1 H), 7.14 (t, J=7.9 Hz, 1 H), 7.06 (t, J=7.6 Hz, 1 H), 5.78 (m, 1 H), 5.39 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, 10.4 Hz, 1 H), 4.41 (s, 1 H), 4.29 (m, 1 H), 4.17 (d, J=11.6 Hz, 1 H), 3.98 (dd, J=11.0, 2.8 Hz, 1 H), 2.92 (m, 1 H), 2.40 (m, 1 H), 2.23 (s, 5 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.43 (s, 10 H), 1.23 (t, J=7.0 Hz, 2 H), 1.05 (m, 2 H), 1.02 (s, 9 H). LC-MS A (retention time: 2.54 ; MS m/z 690 (M+H).



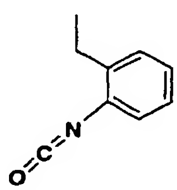
Reagent employed for preparation of Compound 58



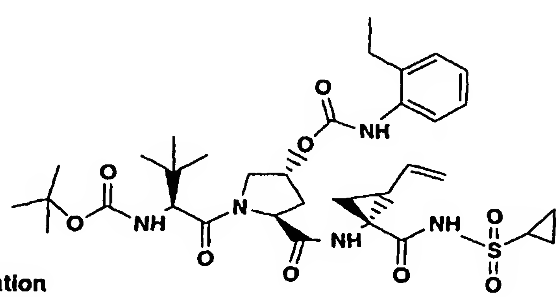
Compound 58

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,6-dimethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(42%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.05 (s, 3 H), 5.78 (m, 1 H), 5.39 (m, 1 H), 5.31 (d, J=17.1 Hz, 1 H), 5.13 (d, J=10.1 Hz, 1 H), 4.44 (dd, J=9.8 Hz, 7.3 Hz, 1 H), 4.30 (m, 1 H), 4.10 (m, 1 H), 4.01 (m, 1 H), 2.93 (m, 1 H), 2.40 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.23 (s, 6 H), 2.18 (m,2 H), 1.87 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.48 (m, 1 H), 1.45 (s, 9 H), 1.23 (t, J=7.3 Hz, 2 H), 1.06 (m, 2 H), 1.03 (s, 9 H). LC-MS A (retention time: 2.55 ; MS m/z 704 (M+H).



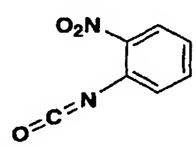
Reagent employed for preparation of Compound 59



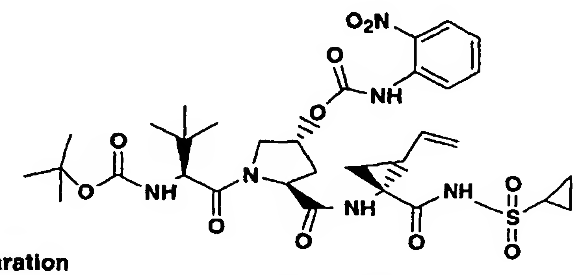
Compound 59

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-ethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(43%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.39 (brs, 1 H), 7.21 (s, J=7.0 Hz, 1 H), 7.14 (m, 2 H), 5.76 (m, 1 H), 5.39 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.11 (d, J=10.1 Hz, 1 H), 4.41 (m, 1 H), 4.29 (m, 1 H), 4.16 (d, J=11.6 Hz, 1 H), 3.98 (d, J=11.6, 1 H), 2.92 (m, 1 H), 2.62 (q, J=7.3 Hz, 2 H), 2.40 (brs, 1 H), 2.20 (m, 2 H), 1.86 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.42 (s, 10 H), 1.23 (m, 2 H), 1.17 (t, J=7.6 Hz, 3 H), 1.03 (s, 11 H). LC-MS A (retention time: 2.61 ; MS m/z 704 (M+H).



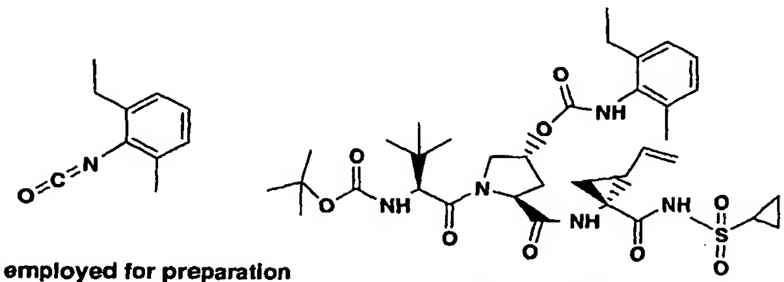
Reagent employed for preparation of Compound 60



Compound 60

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-nitro-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(48%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.31 (d, J=7.9 Hz, 1 H), 8.14 (d, J=8.2 Hz, 1 H), 7.68 (t, J=8.2 Hz, 1 H), 7.24 (t, J=7.3 Hz, 1 H), 6.61 (d, J=8.9 Hz, 1 H), 5.76 (m, 1 H), 5.43 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.11 (d, J=10.4, 1 H), 4.44 (dd, J=10.4 Hz, 7.0 Hz, 1 H), 4.31 (d, J=11.9 Hz, 1 H), 4.23 (d, J=9.5 Hz, 1 H), 3.96 (d, J=8.5 Hz, 1 H), 2.93 (m, 1 H), 2.46 (dd, J=13.7 Hz, 6.7 Hz, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.40 (m, 1 H), 1.31 (s, 9 H), 1.22 (m, 2 H), 1.02 (s, 11 H). LC-MS A (retention time: 2.56 ; MS m/z 721 (M+H).

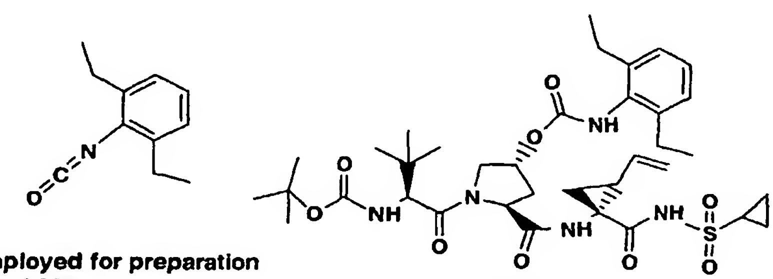


Reagent employed for preparation of Compound 61

Compound 61

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-ethyl-6-methyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(43%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.08 (m, 3 H), 6.64 9d, J=9.2 Hz, 1 H), 5.78 (m, 1 H), 5.40 (s, 1 H), 5.31 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.44 (m, 1 H), 4.31 (d, J=9.5 Hz, 1 H), 4.09 (m, 1 H), 4.00 (m, 1 H), 2.93 (m, 1 H), 2.60 (q, J=7.6 Hz, 2 H), 2.39 (m, 1 H), 2.23 (s, 5 H), 1.87 (dd, J=7.9 Hz, 5.5 Hz, 1 H), 1.50 (s, 1 H), 1.46 (s, 9 H), 1.23 (t, J=7.3 Hz, 2 H), 1.17 (t, J=7.3 Hz, 3 H), 1.03 (s, 11 H). LC-MS A (retention time: 2.63 ; MS m/z 718 (M+H).

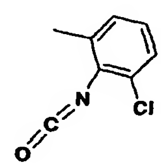


Reagent employed for preparation of Compound 62

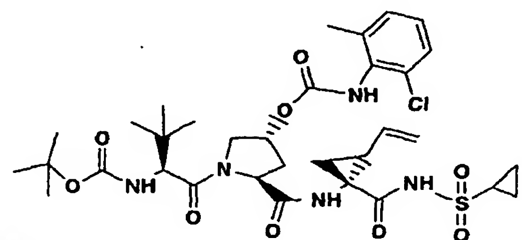
Compound 62

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,6-diethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(51%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.18 (m, 1 H), 7.10 (d, J=7.3 Hz, 2 H), 6.64 (d, J=9.5 Hz, 1 H), 5.78 (m, 1 H), 5.41 (s, 1 H), 5.32 (d, J=17.1 Hz, 1 H), 5.13 (d, J=10.4 Hz, 1 H), 4.44 (dd, J=10.1 Hz, 7.0 Hz, 1 H), 4.32 (d, J=9.5 Hz, 1 H), 4.08 (m, 1 H), 4.01 (m, 1 H), 2.93 (m, 1 H), 2.60 (q, J=7.6, 4 H), 2.40 (m, 1 H), 2.24 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.51 (s, 1 H), 1.46 (s, 9 H), 1.23 (m, 2 H), 1.18 (t, J=7.6 Hz, 6 H), 1.06 (m, 2 H), 1.03 (s, 9 H). LC-MS A (retention time: 2.69 ; MS m/z 732 (M+H).



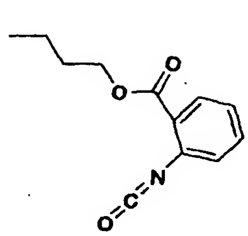
Reagent employed for preparation of Compound 63



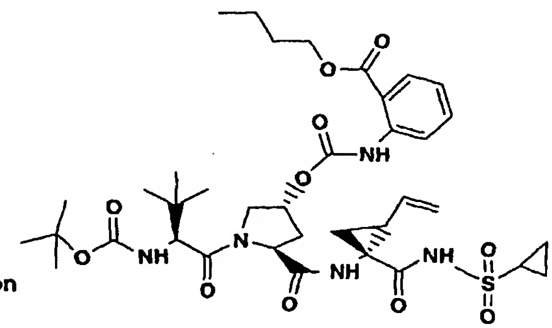
Compound 63

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-chloro-6-methyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(38%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.28 (m, 1 H), 7.18 (m, 2 H), 6.66 (d, J=8.2 Hz, 1 H), 5.77 (m, 1 H), 5.40 (s, 1 H), 5.32 (d, J=16.8 Hz, 1 H), 5.12, (d, J=10.1 Hz, 1 H), 4.44 (m, 1 H), 4.30 (m, 1 H), 4.04 (m, 1 H), 4.01 (m, 1 H), 2.93 (m, 1 H), 2.41 (m, 1 H), 2.29 (s, 3 H), 2.25 (m, 2 H), 1.87 (m, 1 H), 1.49 (m, 1 H), 1.45 (s, 9 H), 1.23 (t, J=7.2, 2 H), 1.06 (m, 2 H), 1.02 (S, 9 H). LC-MS A (retention time: 2.51 ; MS m/z 724 (M+H).



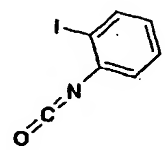
Reagent employed for preparation of Compound 64



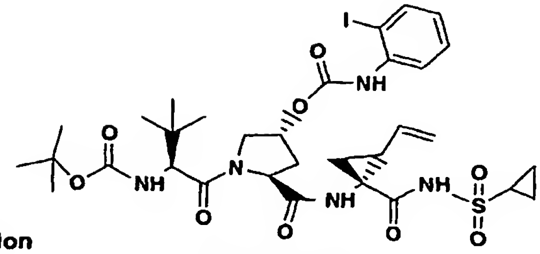
Compound 64

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid butyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(35%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.39 (d, J=8.5 Hz, 1 H), 8.01 (d, J=7.6 Hz, 1 H), 7.56 (t, J=7.6 Hz, 1 H), 7.09 (t, J=7.6 Hz, 1 H), 6.66 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.40 (s, 1 H), 5.31 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.43 (dd, J=10.1 Hz, 7.0 Hz, 1 H), 4.31 (m, 3 H), 4.24 (d, J=9.8 Hz, 1 H), 3.96 (d, J=11.6 Hz, 1 H), 2.94 (m, 1 H), 2.44 (dd, J=13.4 Hz, 6.7 Hz, 1 H), 2.24 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.76 (m, 2 H), 1.48 (q, J=7.6 Hz, 2 H), 1.43 (m, 1 H), 1.29 (s, 9 H), 1.24 (m, 2 H), 1.07 (m, 2 H), 1.02 (s, 9 H), 1.00 (m, 3 H). LC-MS A (retention time: 2.99 ; MS m/z 776 (M+H).



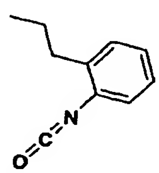
Reagent employed for preparation of Compound 65



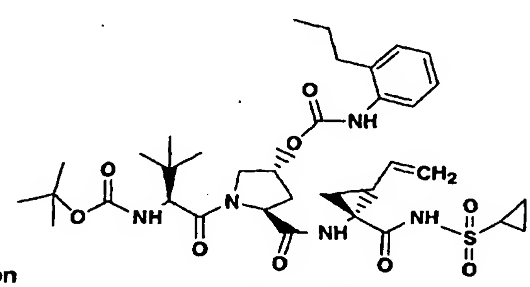
Compound 65

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-iodo-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(36%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.84 (d, J=7.9 Hz, 1 H), 7.57 (brs, 1 H), 7.36 (t, J=7.6 Hz, 1 H), 6.93 (t, J=7.6 Hz, 1 H), 6.63 (d, J=9.2 Hz, 1 H), 5.79 (m, 1 H), 5.38 (s, 1 H), 5.27 (d, J=17.1 Hz, 1 H), 5.08 (d, J=10.1, 1 H), 4.41 (s, 1 H), 4.28 (d, J=9.5 Hz, 1 H), 4.22 (d, J=11.6 Hz, 1 H), 3.99 (dd, J=11.9 Hz, 3.1 Hz, 1 H), 2.90 (m, 1 H), 2.41 (m, 1 H), 2.20 (m, 2 H), 1.85 (J=7.6 Hz, 5.5 Hz, 1 H), 1.40 (s, 10 H), 1.18 (brs, 2 H), 1.01 (s, 11 H). LC-MS A (retention time: 2.60 ; MS m/z 802 (M+H).



Reagent employed for preparation of Compound 66

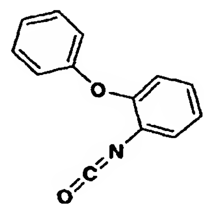


Compound 66

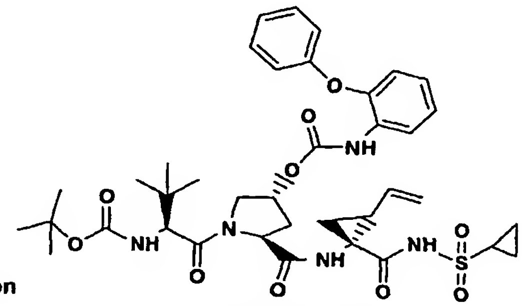
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-propyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(40%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.38 (m, 1 H), 7.19-7.10 (m, 3 H), 6.67 (d, J=9.2 Hz, 1 H), 5.77 (m, 1 H), 5.39 (s, 1 H), 5.31 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.40 (brs, 1 H), 4.29 (d, J=9.5 Hz, 1 H), 4.17 (d, J= 11.9 Hz, 1 H), 3.98 (m,

1 H), 2.91 (m, 1 H), 2.58 (m, 2 H), 2.38 (brs, 1 H), 2.22 (m, 2 H), 1.86 (m, 1 H), 1.58 (q, J=7.3 Hz, 2 H), 1.42 (s, 10 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.03 (s, 9 H), 0.93 (t, J=7.3 Hz, 3 H). LC-MS A (retention time: 2.71 ; MS m/z 718 (M+H).



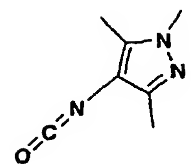
Reagent employed for preparation of Compound 67



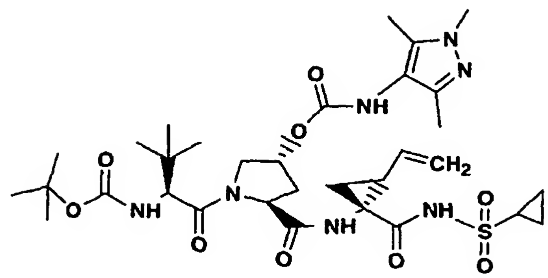
Compound 67

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-phenoxy-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(39%): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.95 (brs, 1 H), 7.34 (t, J=8.2 Hz, 2 H), 7.10 (m, 2 H), 7.02 (t, J=7.9 Hz, 1 H), 6.96 (d, J=8.2 Hz, 2 H), 6.83 (d, J=7.9 Hz, 1 H), 6.62 (d, J=8.9 Hz, 1 H), 5.78 (m, 1 H), 5.35 (s, 1 H), 5.25 (d, J=17.1 Hz, 1 H), 5.07 (d, J=10.4 Hz, 1 H), 4.38 (t, J=9.5 Hz, 1 H), 4.24 (d, J=9.2 Hz, 1 H), 4.17 (d, J=11.9 Hz, 1 H), 3.95 (m, 1 H), 2.89 (m, 1 H), 2.37 (m, 1 H), 2.15 (m, 2 H), 1.84 (m, 1 H), 1.35 (s, 10 H), 1.16 (s, 2 H), 1.01 (s, 11 H). LC-MS A (retention time: 2.80 ; MS m/z 769 (M+H).



Reagent employed for preparation of Compound 68

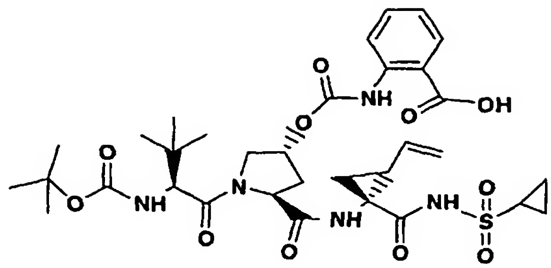


Compound 68

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(1,3,5-Trimethyl-pyrazol-4-yl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane :

^{1}H NMR (d$_4$-MeOH, 500Mz) δ 5.83 (m, 1 H), 5.36 (s, 1 H), 5.27 (d, J=17.4 Hz, 1 H), 5.08 (d, J=9.8 Hz, 1 H), 4.44 (m, 1 H), 4.27 (m, 1 H), 4.10 (m, 1 H), 3.97 (m, 1 H), 3.67 (s, 3 H), 2.84 (m, 1 H), 2.39 (m, 1 H), 2.25 (m, 1 H), 2.18 (m, 1 H), 2.13 (s, 3 H), 2.07 (s, 3 H), 1.85 (m, 1 H), 1.44 (s, 10 H), 1.17 (m, 2 H), 1.03 (m, 11 H). LC-MS C (retention time: 2.21 ; MS m/z 708 (M+H).

Preparation of Compound 69 BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane by hydrolysis of Compound 19, BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid ethyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane:

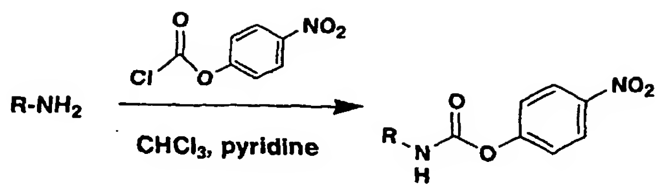


Compound 69

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid ethyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane, compound 19 (82mgs, 0.11 mmol) was dissolved in 600μL THF and 200μL water. LiOH (5.4mgs) was added and the mixture stirred under N_2 for 24 hours. Then more LiOH was added (3.0mgs). The mixture was stirred for 5 days and then more LiOH (5.4 mgs) was added. After another 24 hours, the reaction was diluted with ethyl acetate (25 mL) and washed sequentially with 1N HCl (25 mL) and brine (25 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to yield BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzoic acid))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane 51 mgs (63%) as an off white solid: ^{1}H NMR (d_4-MeOH, 500Mz) δ 8.38 (d, J=8.2 Hz, 1 H), 8.04 (d, J=7.6 Hz, 1 H), 7.54 (t, J=7.3 Hz, 1 H), 7.07 (t, J=7.3 Hz, 1 H), 5.76 (m, 1 H), 5.41 (s, 1 H), 5.30 (d, J=17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.42 (dd, J=10.4 Hz, 7.0 Hz, 1 H), 4.31 (d, J=12.2 Hz, 1 H), 4.22 (d, J=10.1 Hz, 1 H), 3.96 (d, J=11.0 Hz, 1 H), 2.94 (m, 1 H), 2.43 (m, 1 H), 2.23 (m, 2 H), 1.87 (dd, J=8.2 Hz, 5.5 Hz, 1 H), 1.43 (m, 1 H), 1.26 (s, 11 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS A (retention time: 2.61 ; MS m/z 72 (M+H).

Example 5 : Preparation of p-Nitrophenyl carbamate reagents

The scheme below outlines the process used for the formation of a series of p-nitro phenyl carbamates each of which is shown in Table 2. These carbamates are used as reagents for the synthesis of the tripeptide P2 carbamates described in Example 6 and specifically compounds 70 through 74.

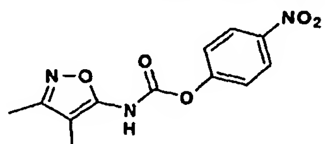
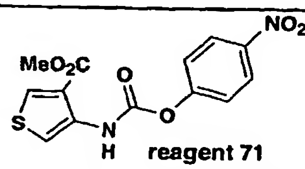
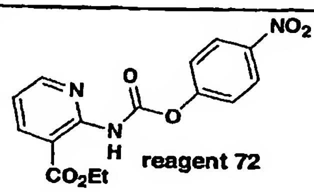
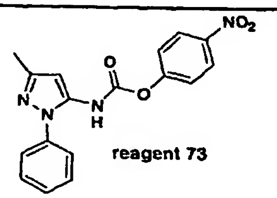
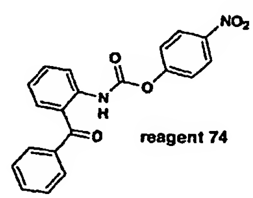


general structure of a p-nitrophenyl carbamate:

The following general procedure was used to prepare the p-nitrophenyl carbamate reagents found in Table 2.

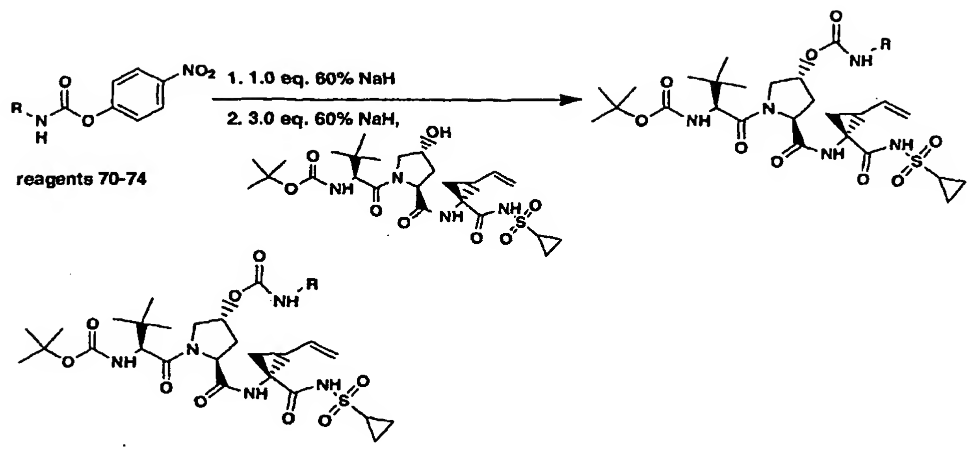
The starting heterocyclic amine (1.34 mmol) was dissolved in 10 mL $CHCl_3$. To this solution was added a solution of p-NO_2 phenyl chloroformate (270 mgs, 1.34 mmol) dissolved in 10 mL $CHCl_3$ followed by pyridine (108 mL). After stirring for two hours the reaction was filtered and then concentrated *in vacuo*. The desired heterocyclic p-nitrophenyl carbamates were taken on to the next step without further purification.

Table 2:

p-NO_2-phenyl carbamate reagent	Yield
 reagent 70	85%
 reagent 71	98%
 reagent 72	82%
 reagent 73	77%
 reagent 74	97%

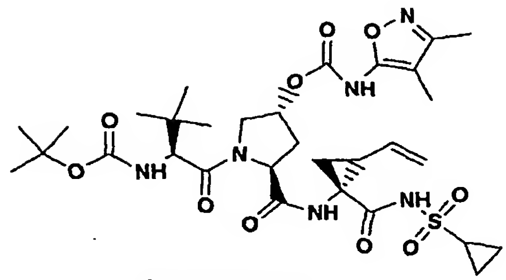
Example 6: Preparation of tripeptide P2 carbamates ,Compounds 70 through 74.

The above p-nitro phenyl carbamates (reagents 70-74) listed in table 2 were used to prepare the carbamate tripeptides (Compounds 70-74) of Example 6 following the general procedure described below:



General procedure for formation of tripeptide carbamates Compounds 70 through 74 using reagents 70 –74 found in table 2.

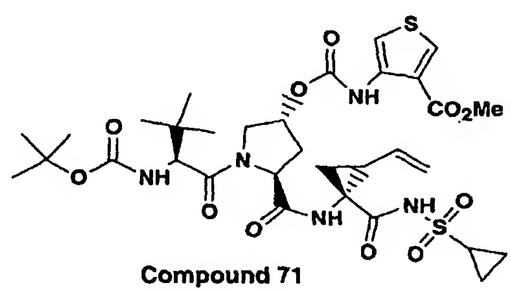
Sodium hydride (60%, 17 mgs, 0.432mmol) was added to a precooled solution (2°C) of BocNH-P3(t-BuGly)-P2(Hyp)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$.Cyclopropane (80 mgs, 0.144 mmol) dissolved in 2.0 mL tetrahydrofuran. In a separate flask, 60% NaH (6.5 mgs, 0.165mmol) was added to a solution of the heterocyclic p-NO$_2$ phenyl carbamate (0.158 mmol, reagent 70-74 found in table 2) dissolved in 500uL THF and 200uL DMF (Procedure A) or 500uL DMF (Procedure B). This solution was stirred for 5 minutes and then was syringed directly into the precooled tripeptide mixture. The reaction was stirred for 4 hours and then quenched with saturated ammonium chloride solution (1.0 mL). The reaction was then diluted with 50 mL ethyl acetate and washed with 50 mL 1N HCl, 50 mL 1N NaHCO$_3$, 50 mL water and 50 mL brine. The product was purified by Prep TLC eluting with 2:1 ethyl acetate: hexanes to yield the following tripeptide carbamates:



Compound 70

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3,4-Dimethyl-isoxazol-5-yl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(69%, procedure A, using reagent 70): ^{1}H NMR (d_4-MeOH, 500Mz) δ 6.59 (m, 1H, NH), 5.83 (m, 1H), 5.40 (m, 1H), 5.26 (d, 1H, J=16.8 Hz), 5.09 (m, 1H), 4.40 (m, 1H), 4.26 (m, 1H), 4.18 (d, 1H, J=11.9 Hz), 3.97 (dd, 1H, J=12.2, 3.7 Hz), 2.85 (bs, 1H), 2.42 (m, 1H), 2.20-2.30 (m, 2H), 2.18 (s, 3H), 1.87 (s, 3H), 1.86 (m, 2H), 1.42 (s, 9H), 1.39 (m, 2H), 1.15-1.21 (m, 2H), 1.03 (s, 9H). LC-MS C (retention time: 2.27; MS m/z 695 (M+H).

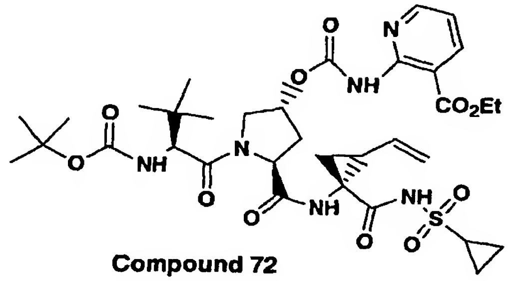


Compound 71

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-4-(thiophene-3-carboxylic acid methyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

(21%, procedure B, using reagent 71): ^{1}H NMR (d_4-MeOH, 300Mz) δ 8.21 (d, 1H, J=3.7 Hz), 7.62 (bs, 1H), 6.65 (d, 1H, NH, J=8.8 Hz), 5.81 (m, 1H), 5.40 (bs, 1H), 5.27 (d, 1H, J=17.2 Hz), 5.09 (d, 1H, J=10.9 Hz), 4.45 (m, 1H), 4.30 (m, 1H), 4.22 (m, 1H), 3.95 (m, 1H), 3.86 (s, 3H), 2.87 (m, 1H), 2.46 (m, 1H), 2.21 (m, 2H), 1.87

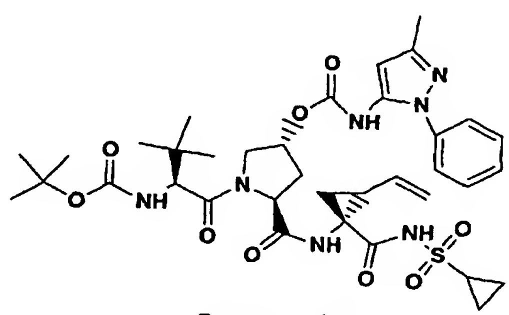
(m, 1H), 1.30 (s, 9H), 1.26-1.36 (m, 2H), 1.15-1.22 (m, 2H), 1.02 (s, 9H). LC-MS C (retention time: 2.62 ; MS m/z 740 (M+H).



Compound 72

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-(nicotinic acid ethyl ester))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane

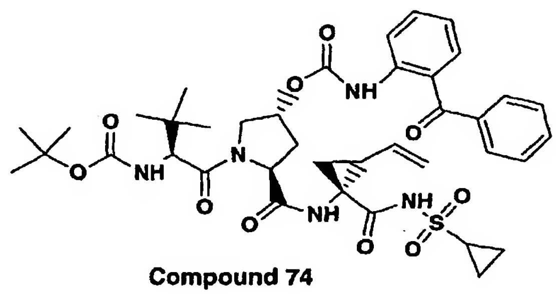
(13%, procedure A, using reagent 72): ^{1}H NMR (d$_4$-MeOH, 500Mz) δ 8.48 (m, 1H), 8.38 (m, 1H), 7.18 (m, 1H), 5.83 (m, 1H), 5.44 (m, 1H), 5.27 (d, 1H, J=17.1 Hz), 5.08 (m, 1H), 4.45 (m, 1H), 4.38 (q, 2H, J=7.0 Hz), 4.30 (m, 1H), 4.23 (m, 1H), 3.98 (m, 1H), 2.85 (m, 1H), 2.47 (m, 1H), 2.15-2.28 (m, 2H), 2.01 (m, 1H), 1.85 (m, 1H), 1.44 (m, 2H), 1.39 (t, 3H, J=7.0 Hz), 1.32 (s, 9H), 1.18 (m, 2H), 1.03 (s, 9H). LC-MS C (retention time: 2.38 ; MS m/z 749 (M+H).



Compound 73

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Methyl-2-phenyl-4H-pyrazol-3-yl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$ Cyclopropane

(4.2%, procedure A, using reagent 73): ^{1}H NMR (d_4-MeOH, 300Mz) δ 7.48 (m, 5H), 6.67 (d, 1H, J=10.3 Hz), 6.21 (bs, 1H), 5.76 (m, 1H), 5.31 (d, 1H, J=17.2 Hz), 5.30 (m, 1H), 5.13 (dd, 1H, J=10.3, 1.5 Hz), 4.19-4.31 (m, 2H), 4.05 (m, 1H), 3.89-3.94 (m, 1H), 2.93 (m, 1H), 2.26 (s, 3H), 2.18-2.28 (m, 2H), 1.86 (m, 1H), 1.42 (s, 9H), 1.37-1.44 (m, 2H), 1.23-1.29 (m, 2H), 1.04-1.10 (m, 2H), 1.00 (s, 9H). LC-MS C (retention time: 2.40 ; MS m/z 756 (M+H).

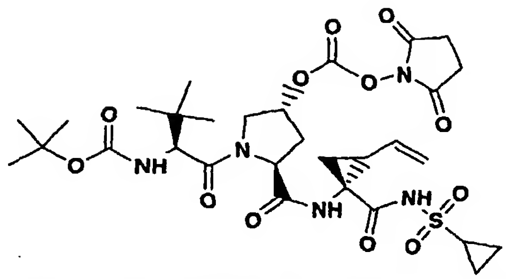


Compound 74

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-benzophenone))))-P1(*1R,2S* VinylAcca)-CONHSO$_2$Cyclopropane

(37%, using reagent 74): ^{1}H NMR (d_4-MeOH, 300Mz) δ 8.13 (d, 1H, J=8.05 Hz, 7.48-7.69 (m, 7H), 7.15 (t, 1H, J=7.3 Hz), 6.66 (d, 1H, J=9.2 Hz), 5.80 (m, 1H), 5.34 (m, 1H), 5.26 (d, 1H, J=17.2 Hz), 5.08 (d, 1H, J=10.6 Hz), 4.40 (m, 1H), 4.21 (m, 2H), 3.94 (dd, 1H, J=11.7, 3.3 Hz), 2.86 (bs, 1H), 2.37 (m, 1H), 2.19 (m, 2H), 1.86 (m, 1H), 1.37-1.44 (m, 2H), 1.30 (s, 9H), 1.18 (m, 2H), 1.01 (s, 9H), 0.94 –1.02 (m, 1H). LC-MS C (retention time: 2.76 ; MS m/z 780 (M+H).

Example 7: Preparation of BocNH-P3(t-BuGly)-P2(Hyp(O-CO-Osuccinimidyl))-P1(*1R,2S* VinylAcca)-CONHSO$_2$Cyclopropane for use as an intermediate in the synthesis of the tripeptide P2 carbamates found in Example 8.



P2 succinimidyl carbonate intermediate used for preparation of tripepetide carbamates found in Example 8

BocNH-P3(t-BuGly)-P2(Hyp)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$-Cyclopropane (400 mgs, 0.710 mmol, 1.0 eq.) was dissolved in tetrahydrofuran (10mL). 90% *N,N'*-Disuccinimidyl Carbonate (404 mgs, 1.42 mmol, 2.0 eq.) added to form a suspension. To well stirred suspension, 60% NaH (88 mgs, 2.20 mmol, 3.1 eq.) was added and the reaction refluxed for 4 hours. The reaction was then diluted with ethyl acetate (125 mL), and washed with 1N HCl (125 mL) and brine (125 mL). The organic layer was dried over sodium sulfate, filtered, and solvent removed *in vacuo* to yield the titled product as an off white foam which was taken on without purification. Crude yield 100%. LC-MS C (retention time: 2.01 ; MS m/z 698 $(M+H)^+$.

Example 8: Preparation of tripeptide P2-carbamates (BocNH-P3(t-BuGly)-P2(Hyp(O-CO-NHR)-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$-Cyclopropane, Compounds 75-86 using the P2 succinimidyl carbonates described in Example 7:

The product of example 7, BocNH-P3(t-BuGly)-P2(Hyp(O-CO-succinimidyl))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (90% estimated purity, 145 mgs, 0.188 mmol, 1.0 eq.), was dissolved in dichloromethane (2.0 mL) and an amine was then added as for example 2-amino pyridine (35.4 mgs, 0.376 mmol, 2.0 eq.). The pressure tube was sealed and heated to 50°C for three days. It should be noted that the 2-amino pyridine reagent described above was used to prepare compound 75 of Example 8. In the preparation of compounds 76-86 of example 8 the requisite amine

was used in place of said 2-amino pyridine. The crude material was purified by one of the two methods outlined below:

Method A: The crude material was loaded directly onto a preparative TLC plate (Analtech SiO_2, 1000μns) and eluted in 1:2 hexanes:EtOAc. The absorbed material/SiO_2 was scraped off the plate and stirred with 20% methanol in ethyl acetate for 1 hour. The silica was filtered away and the liquid concentrated *in vacuo* to yield the product.

Method B: The crude reaction mixture was concentrated *in vacuo* and residue dissolved in methanol (2.0mL) and passed through a 0.2μm PTFE syringe filter. This solution was then injected directly on to the preparative HPLC with the following parameters.

Column: XTerra Prep MS C18 (19.0 x 100.0mm)

Gradient: 50% solvent A/ 50% solvent B to 0% solvent A/ 100% solvent B

Gradient time: 15 min

Hold time: 5 min

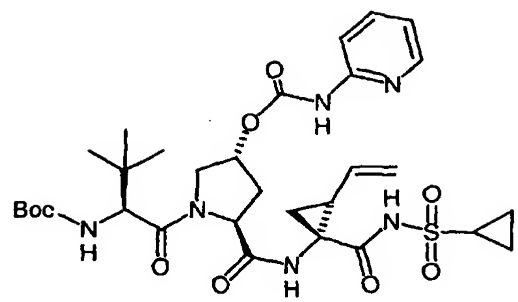
Flow rate: 25mL/min

Detector Wavelength: 220

Solvents: Solvent A: 10% methanol/ 90% water/ 10nM ammonium acetate.

Solvent B: 90% methanol/ 10% water/ 10nM ammonium acetate.

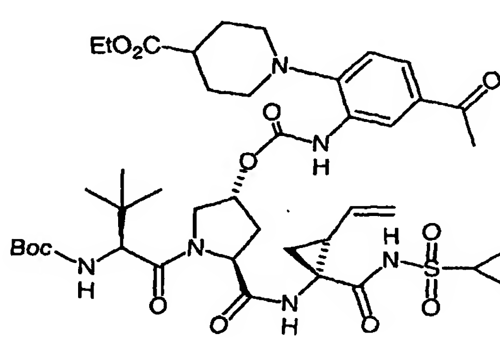
After the run, the fractions were concentrated to remove the methanol and then poured into equal volumes of water and ethyl acetate. The organic layer was dried with sodium sulfate and concentrated *in vacuo* to yield the purified products:



compound 75

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(pyridin-2-yl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method A, 8%):

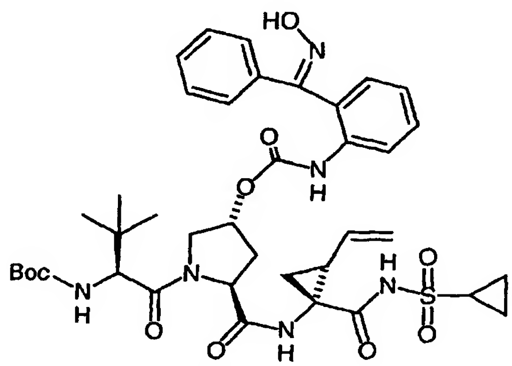
^{1}H NMR (d$_4$-MeOH, 300Mz) δ 8.20 (d, 1H, J=4.0 Hz), 7.88 (app. d, 1H), 7.74 (t, 1H, J=6.9 Hz), 7.04 (t, 1H, J=6.0 Hz), 6.64 (d, 1H, NH, J=8.8 Hz), 5.78 (m, 1H), 5.43 (m, 1H), 5.27 (d, 1H, J=17.2 Hz), 5.09 (d, 1H, J=10.2 Hz), 4.42 (t, 1H), 4.25 (m, 2H), 3.99 (dd, 1H), 2.90 (m, 1H), 2.44 (m, 1H), 2.20 (m, 2H), 1.86 (m, 1H), 1.30-1.43 (m, 3H), 1.30 (s, 9H), 1.19 (m, 2H), 1.02 (s, 9H), 1.61-1.82 (m, 1H). LC-MS F (retention time: 2.66 ; MS m/z 677 (M+H).



Compound 76

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-(1-(4-acetyl-phenyl))-piperidine-4-carboxylic acid ethyl ester)))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 32%):

^{1}H NMR (d_4-MeOH, 500Mz) δ 8.47 (s, 1H), 7.73 (d, 1H, J=8.2 Hz), 7.20 (d, 1H, J=8.6 Hz), 6.62 (d, 1H, NH, J=9.2 Hz), 5.77 (m, 1H), 5.44 (m,1 H), 5.31 (d, 1H, J=17.1 Hz), 5.13 (dd, 1H, J=10.4, 1.5 Hz), 4.45 (m, 1H), 4.26 (m, 2H), 4.18 (q, 2H, J=7.0 Hz), 4.01-4.14 (m, 2H), 3.12 (m, 2H), 2.94 (m, 1H), 2.80 (t, 1H, J=11.4 Hz), 2.72 (t, 1H, J=11.9 Hz), 2.56 (s, 3H), 2.43-2.53 (m, 2H), 2.18-2.28 (m, 2H), 2.01-2.04 (m, 3H), 1.79-1.91 (m, 3H), 1.44 (m, 2H), 1.32 (s, 9H), 1.21-1.29 (m, 2H), 1.07 (m, 1H), 1.03 (s, 9H). LC-MS C (retention time: 2.71 ; MS m/z 873 (M+H).



Compound 77

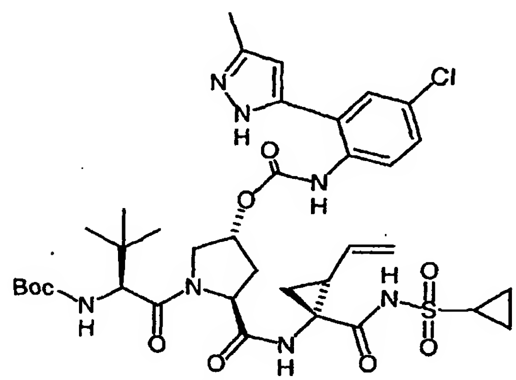
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-(benzophenone oxime))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (isomer A, purified by method B, 23%):

^{1}H NMR (d_4-MeOH, 500Mz) δ 7.43 (m, 3H), 7.33 (m, 3H), 7.21 (t, J=8.9 Hz), 5.78 (m, 1H), 5.25-5.30 (m, 2H), 5.09 (dd, 1H, J=10.5, 1.7 Hz), 4.56 (m, 1H), 4.32 (m, 1H), 4.24 (m, 1H), 4.12 (m, 1H), 3.94 (m, 1H), 2.89 (m, 1H), 2.29 (m, 1H), 2.16 (m, 2H), 1.95 (d, 1H, J=12.8 Hz), 1.84 (m, 1H), 1.37 (s, 9H), 1.19 (m, 2H), 1.00 (s, 9H), 0.96-1.04 (m, 2H). LC-MS C (retention time: 2.70 ; MS m/z 795 (M+H).

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-(benzophenone oxime))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (isomer B, purified by method B, 19%):

^{1}H NMR (d_4-MeOH, 500Mz) δ 8.13 (s, 1H, OH), 7.43 (m, 3H), 7.29 (m, 3H), 6.94 (m, 2H), 6.67 (d, 1H, NH, J= 9.2 Hz), 5.78 (m, 1H), 5.41 (m, 1H), 5.28 (d, 1H, J=17.1 Hz), 5.10 (d, 1H, J=11.6 Hz), 4.57 (m, 1H), 4.38 (m, 1H), 4.26 (m, 1H), 4.17

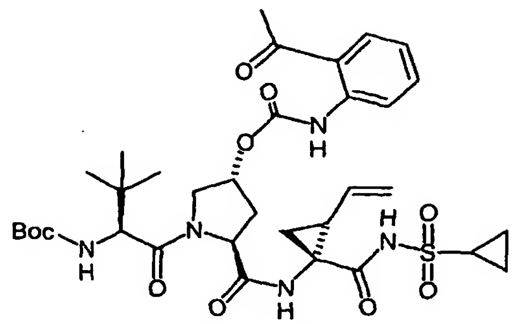
(app. d, 1H), 3.99-4.05 (m, 1H), 2.92 (m, 1H), 2.37 (dd, 1H, J=14.0, 7.0 Hz), 2.20 (m, 2H), 1.95 (d, 1H, J=16.8 Hz), 1.87 (m, 1H), 1.40-1.44 (m, 2H), 1.36 (s, 9H), 1.20-1.25 (m, 2H), 1.03 (s, 9H). LC-MS C (retention time: 2.83 ; MS m/z 795 (M+H).



Compound 78

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-1-(4-Chloro-2-(5-methyl-2H-pyrazol-3-yl)phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 11%):

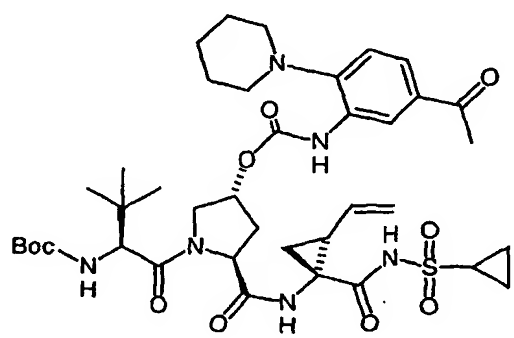
^{1}H NMR (d_4-MeOH, 500Mz) δ 8.23 (m, 1H), 7.62 (s, 1H), 7.23 (dd, 1H, J=8.5, 2.4 Hz), 6.62 (d, 1H, NH, J-7.6 Hz), 6.46 (s, 1H), 5.78 (m, 1H), 5.42 (m, 1H), 5.27 (d, 1H), 5.10 (d, 1H), 4.56 (m, 1H), 4.42 (m, 1H), 4.24 (m, 2H), 4.04 (dd, 1H, J=12.0, 3.2 Hz), 2.92 (m, 1H), 2.40 (m, 1H), 2.35 (s, 3H), 2.15-2.27 (m, 2H), 1.86 (dd, 1H, J=7.9, 5.5Hz), 1.42 (m, 2H), 1.26 (s, 9H), 1.21 (m, 2H), 1.02 (s, 9H). LC-MS G (retention time: 3.06; MS m/z 790 (M+H).



Compound 79

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-acetophenone))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 14%):

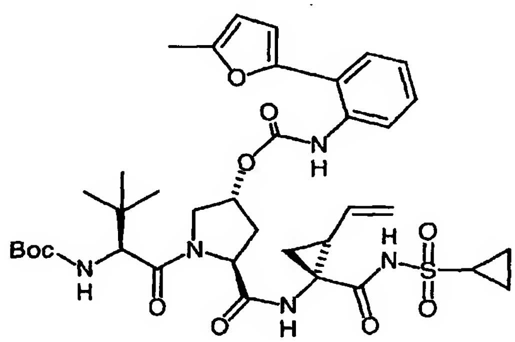
^{1}H NMR (d_4-MeOH, 500Mz) δ 8.40 (d, 1H, J=8.6 Hz), 8.02 (d, 1H, J=7.9), 7.56 (t, 1H, J=8.6), 7.17 (t, 1H, J=7.5 Hz), 6.62 (d, 1H, NH, J=9.5 Hz), 5.78 (m, 1H), 5.39 (s, 1H), 5.28 (d, 1H, J=17.1 Hz), 5.10 (d, 1H, J=10.4, 1.8 Hz), 4.45 (m, 1H), 4.31 (d, 1H, J=4.9 Hz), 4.24 (d, 1H, J=4.3 Hz), 4.05 (m, 1H), 3.97 (m, 1H), 2.91 (m, 1H), 2.63 (s, 3H), 2.45 (dd, 1H, J=13.7, 7.0 Hz), 2.17-2.28 (m, 2H), 1.87 (m, 1H), 1.38-1.45 (m, 2H), 1.28 (s, 9H), 1.17-1.25 (m, 2H), 1.02 (s, 9H). LC-MS C (retention time: 2.62 ; MS m/z 718 (M+H).



Compound 80

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-1-(2-piperidino-5-acetylphenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 18%):

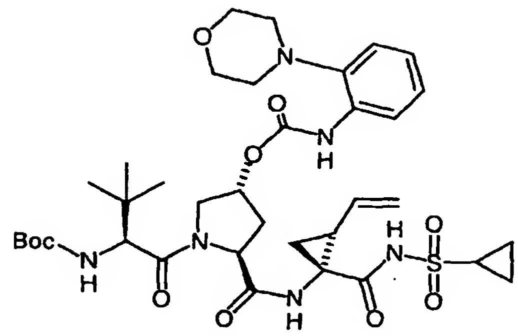
^{1}H NMR (d_4-MeOH, 500Mz) δ 8.51 (bs, 1H), 7.70 (d, 1H, J=8.2 Hz), 7.18 (d, 1H, J=8.6 Hz), 5.85 (m, 1H), 5.42 (s, 1H), 5.23 (d, 1H, J=17.1 Hz), 5.05 (d, 1H, J=10.4 Hz), 4.48 (m, 1H), 4.45 (m, 2H), 4.01-4.12 (m, 2H), 2.80-2.92 (m, 4H), 2.55 (s, 3H), 2.50 (m, 1H), 2.35 (m, 1H), 2.14 (m, 1H), 1.85 (m, 1H), 1.74 (m, 5H), 1.62 (m, 2H), 1.32 (s, 9H), 1.13 (m, 2H), 1.02 (s, 9H), 0.95 (m, 2H) . LC-MS C (retention time: 2.75 ; MS m/z 801 (M+H).



Compound 81

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-[(5-Methyl-furan-2-yl)-phenyl]))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 5%):

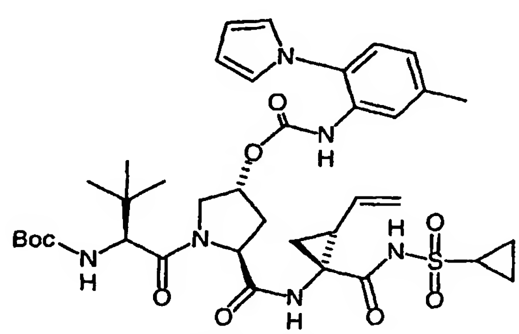
^{1}H NMR (d_4-MeOH, 500Mz) δ 7.63 (d, 2H, J=7.9 Hz), 7.24 (t, 1H, J=7.6), 7.19 (t, 1H, J=7.2 Hz), 8.58 (d, 1H, J=3.0 Hz), 6.14 (d, 1H, J=3.0 Hz), 5.83 (m, 1H), 5.37 (m, 1H), 5.25 (m, 1H), 5.07 (m, 1H), 4.41 (m, 1H), 4.26 (m, 1H), 4.19 (m, 1H), 3.98 (m, 1H), 2.87 (m, 1H), 2.36 (s, 3H), 2.15 (m, 1H), 1.84 (m, 1H), 1.37 (s, 9H), 1.29 (m, 2H), 1.16 (m, 2H), 1.03 (s, 9H), 0.90-0.97 (m, 3H). LC-MS C (retention time: 2.81 ; MS m/z 756 (M+H).



Compound 82

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-(morpholin-4-yl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 22%):

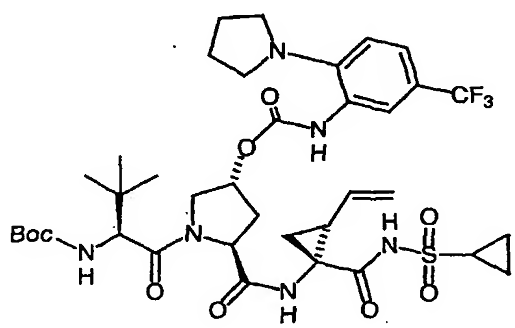
^{1}H NMR (d$_4$-MeOH, 300Mz) δ 7.89 (bs, 1H), 7.20 (d, 1H, J=7.7 Hz), 7.03-7.13 (m, 1H), 6.71 (d, 1H, J=9.9 Hz), 5.76 (m, 1H), 5.41 (m, 1H), 5.31 (d, 1H, J=17.2 Hz), 5.13 (d, 1H, J=10.3 Hz), 4.41 (m, 1H), 4.25 (m, 2H), 3.99 (m, 1H), 3.83 (m, 4H), 2.95 (m, 1H), 2.83 (m, 4H), 2.41 (m, 1H), 2.15-2.29 (m, 2H), 1.89 (m, 1H), 1.44 (m, 1H), 1.36 (s, 9H), 1.24 (m, 2H), 1.07 (m, 2H), 1.03 (m, 9H). LC-MS C (retention time: 2.71 ; MS m/z 761 (M+H).



Compound 83

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Methyl-2-pyrrol-1-yl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method B, 18%):

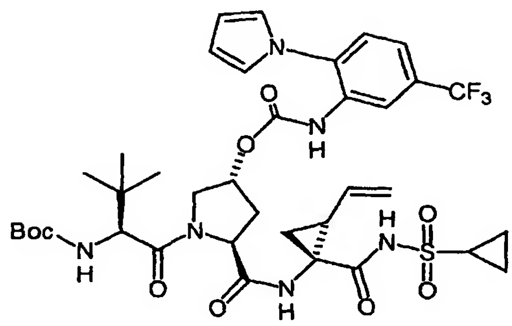
^{1}H NMR (d_4-MeOH, 300Mz) δ 7.59 (bs, 1H), 7.16 (d, 1H, J=8.05 Hz), 7.06 (dd, 1H, J=, 8.05, 1.1 Hz), 6.80 (m, 2H), 6.67 (d, 1H, J=9.5 Hz), 6.26 (m, 2H), 5.77 (m, 1H), 5.28-5.34 (m, 2H), 5.12 (m, 1H), 4.23-4.32 (m, 2H), 4.10 (m, 1H), 3.92 (m, 1H), 2.93 (m, 1H), 2.37 (s, 3H), 2.23 (m, 2H), 2.10 (m, 1H), 1.87 (m, 1H), 1.40 (s, 9H), 1.21-1.31 (m, 3H), 1.04-1.10 (m, 2H), 1.01 (s, 9H). LC-MS C (retention time: 2.84 ; MS m/z 755 (M+H).



Compound 84

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-Pyrrolidin-1-yl-5-trifluoromethyl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method A, 23%):

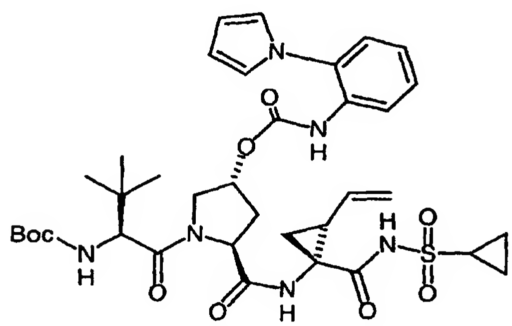
^{1}H NMR (d_4-MeOH, 500Mz) δ 7.59 (bs, 1H), 7.30 (m, 1H), 6.93 (m, 1H), 5.86 (m, 1H), 5.39 (m, 1H), 5.23 (m, 1H), 5.04 (m, 1H), 4.45 (m, 1H), 4.11-4.29 (m, 2H), 4.01 (m, 1H), 2.66-2.87 (m, 1H), 2.29-2.58 (m, 2H), 2.12 (m, 1H), 1.95 (m, 5H), 1.83 (m, 1H), 1.38-1.44 (m, 2H), 1.39 (s, 9H), 1.12 (m, 2H), 1.02 (s, 9H), 0.86-1.07 (m, 4H). LC-MS C (retention time: 2.86 ; MS m/z 813 (M+H).



Compound 85

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-pyrrolidin-1-yl-5-trifluoromethyl–phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$ Cyclo propane (purified by Method A, 25%):

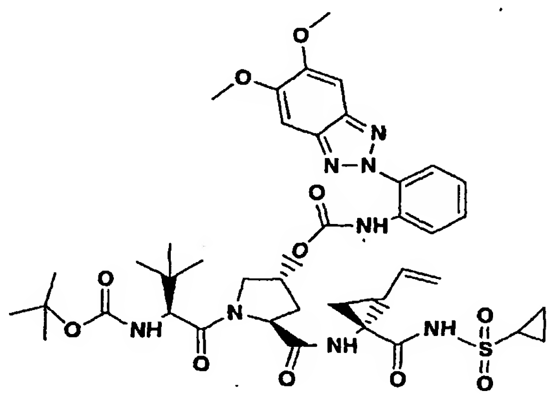
^{1}H NMR (d$_4$-MeOH, 500Mz) δ 7.52 (d, 1H, J=8.2 Hz), 7.46 (d, 1H, J=8.2 Hz), 6.92 (s, 2H), 6.34 (s, 2H), 5.84 (m, 1H), 5.30 (m, 1H), 5.19 (m, 1H), 5.00 (m, 1H), 4.37 (m, 1H), 4.20 (m, 2H), 4.04-4.11 (m, 1H), 3.98 (m, 1H), 3.89 (m, 1H), 2.82 (m, 1H), 2.30-2.36 (m, 2H), 1.80 (m, 1H), 1.44 (m, 2H), 1.35 (s, 9H), 1.28 (m, 2H), 1.01 (s, 9H), 0.81-0.93 (m, 1H). LC-MS C (retention time: 2.87 ; MS m/z 809 (M+H).



Compound 86

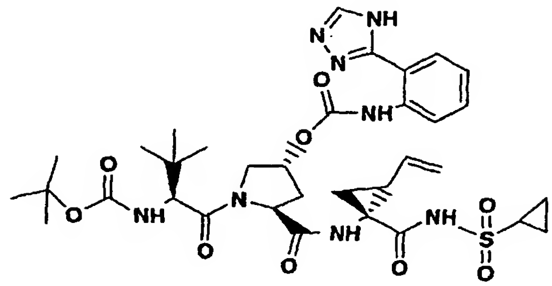
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-pyrrol-1-yl-phenyl))))-P1(1*R*,2*S* VinylAcca)-CONHSO$_2$Cyclopropane (purified by Method A, 41%):

^{1}H NMR (d$_4$-MeOH, 300Mz) δ 7.76 (bs, 1H), 7.21-7.37 (m, 4H), 6.84 (s, 2H), 6.56 (d, 1H, J=8.4 Hz), 6.28 (m, 2H), 5.86 (m, 1H), 5.25 (m, 1H), 5.18 (bs, 1H), 5.03 (d, 1H, J=10.6 Hz), 4.35 (m, 1H), 4.22 (, 1H), 4.08 (m, 1H), 3.86-3.96 (m, 1H), 2.79 (m, 1H), 2.25-2.36 (m, 2H), 2.08 (m, 1H), 1.82 (m, 1H), 1.39 (s, 9H), 1.28-1.35 (m, 1H), 1.10 (m, 1H), 1.01 (s, 9H), 0.91 (m, 1H). LC-MS F (retention time: 3.36; MS m/z 741 (M+H).



Compound 87

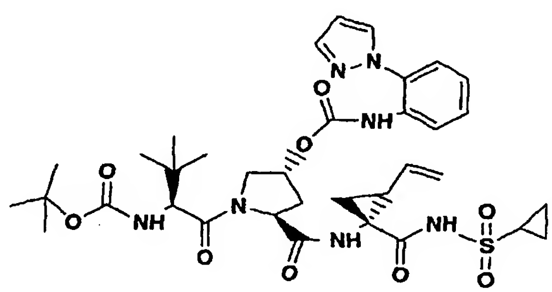
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-(5,6-Dimethoxy-benzotriazol-2-yl)-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method A, 29%): ^{1}H NMR (MeOH) δ 8.30 (d, J=7.0 Hz, 1 H), 8.07 (d, J=8.4 Hz, 1 H), 7.42 (m, 1 H), 7.22 (m, 3 H), 6.58 (d, J=9.5 Hz, 1 H), 5.76 (m, 1 H), 5.40 (s, 1 H), 5.28 (dd, J=1.5 Hz, 17.2 Hz, 1 H), 5.10 (dd, J=1.8 Hz, 10.3 Hz, 1 H), 4.44 (dd, J=7.0 Hz, 9.9 Hz, 1 H), 4.25 (m, 2 H), 3.97 (m, 7 H), 2.92 (m, 1 H), 2.43 (m, 1 H), 2.20 (m, 2 H), 1.87 (dd, J=5.5 Hz, 8.1 Hz, 1 H), 1.43 (m, 1 H), 1.19 (m, 11 H), 1.01 (m, 11 H). LC-MS C (retention time: 2.71 ; MS m/z 853 (M+H).



Compound 88

Compound 88

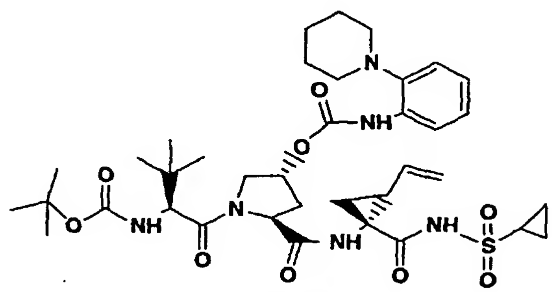
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-(4H-[1,2,4]Triazol-3-yl)-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 31%): ^{1}H NMR (MeOH) δ 8.56 (brs, 1 H), 8.34 (brs, 1 H), 8.15 (brs, 1 H), 7.39 (brs, 1 H), 7.13 (s, 1 H), 6.65 (d, J=9.5 Hz, 1 H), 5.76 (m, 1 H), 5.43 (s, 1 H), 5.31 (dd, J=1.2 Hz, 17.1 Hz, 1 H), 5.13 (dd, J=1.5 Hz, 10.4 Hz, 1 H), 4.44 (dd, J=7.3 Hz, 10.1 Hz, 1 H), 4.30 (d, J=11.3 Hz, 1 H), 4.25 (m, 1 H), 3.99 (m, 1 H), 2.94 (m, 1 H), 2.43 (q, J=6.4 Hz, 1 H), 2.22 (m, 2 H), 1.88 (dd, J=5.5 Hz, 8.2 Hz, 1 H), 1.43 (m, 1 H), 1.24 (m, 11 H), 1.08 (m, 2 H), 1.02 (s, 9 H). LC-MS C (retention time: 2.45 ; MS m/z 743 (M+H).



Compound 89

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-Pyrazol-1-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 53%): ^{1}H NMR (MeOH) δ 8.08 (brs, 1 H), 8.03 (d, J=1.8 Hz, 1 H), 7.76 (d, J=1.5 Hz, 1 H), 7.45 (d, J=7.9 Hz, 1 H),

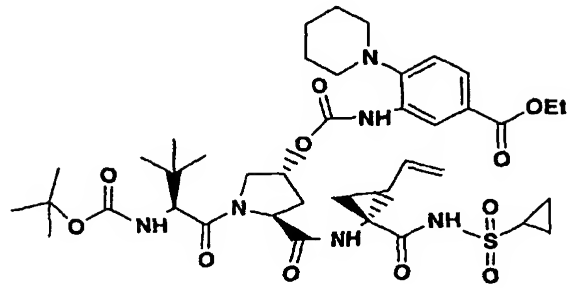
7.37 (t, J=8.6 Hz, 1 H), 7.21 (t, J=7.9 Hz, 1 H), 6.60 (d, J=9.2 Hz, 1 H), 6.54 (t, J=2.1 Hz, 1 H), 5.76 (m, 1 H), 5.35 (s, 1 H), 5.30 (dd, J=1.5 Hz, 17.1 Hz, 1 H), 5.12 (d, J=10.1 Hz, 1 H), 4.36 (m, 1 H), 4.24 (d, J=9.5 Hz, 1 H), 4.19 (d, J=11.9 Hz, 1 H), 3.95 (dd, J=2.8 Hz, 11.6 Hz, 1 H), 2.93 (m, 1 H), 2.36 (m, 1 H), 2.22 (q, J=8.9 Hz, 1 H), 2.16 (m, 1 H), 1.87 (m, 1 H), 1.44 (m, 1 H), 1.34 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS C (retention time: 2.44 ; MS m/z 742 (M+H).



Compound 90

Compound 90

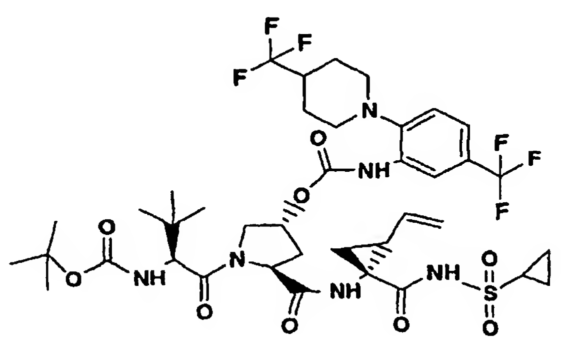
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-Piperidin-1-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 49%): ^{1}H NMR (MeOH) δ 7.91 (brs, 1 H), 7.16 (d, J=7.6 Hz, 1 H), 7.07 (t, J=7.6 Hz, 1 H), 7.01 (t, J=7.6 Hz, 1 H), 6.61 (d, J=9.2 Hz, 1 H), 5.76 (m, 1 H), 5.41 (s, 1 H), 5.30 (dd, J=1.5 Hz, 17.1 Hz, 1 H), 5.12 (dd, J=1.5 Hz, 10.4 Hz, 1 H), 4.42 (m, 1 H), 4.25 (m, 2 H), 3.99 (dd, J=3.4 Hz, 11.9 Hz, 1 H), 2.93 (m, 1 H), 2.76 (m, 4 H), 2.44 (m, 1 H), 2.23 (m, 2 H), 1.87 (dd, J=5.5 Hz, 8.2 Hz, 1 H), 1.72 (m, 4 H), 1.59 (m, 2 H), 1.43 (m, 1 H), 1.34 (s, 9 H), 1.24 (m, 2 H), 1.07 (m, 2 H), 1.03 (s, 9 H). LC-MS C (retention time: 2.37 ; MS m/z 759 (M+H).



Compound 91

Compound 91

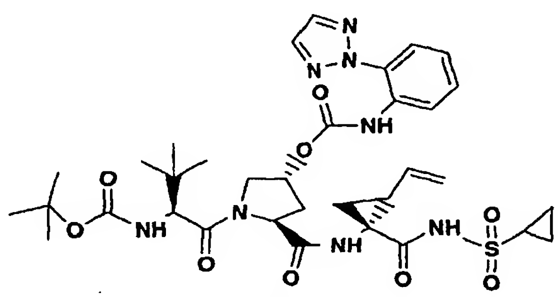
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-carboxyethyl-2-piperidin-1-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 43%): ^{1}H NMR (MeOH) δ 8.53 (s, 1 H), 7.71 (d, J=8.2 Hz, 1 H), 7.18 (d, J=8.2 Hz, 1 H), 6.58 (d, J=8.9 Hz, 1 H), 5.77 (m, 1 H), 5.43 (s, 1 H), 5.30 (d, J=17.4 Hz, 1 H), 5.12 (dd, J=1.8 Hz, 10.4 Hz, 1 H), 4.43 (m, 1 H), 4.34 (dd, J=7.0 Hz, 14.3 Hz, 2 H), 4.25 (m, 2 H), 4.00 (m, 1 H), 2.93 (m, 1 H), 2.84 (m, 4 H), 2.45 (dd, JJ=7.0 Hz, 13.7 Hz, 1 H), 2.23 (m, 2 H), 1.87 (dd, J=5.5 Hz, 8.2 Hz, 1 H), 1.73 (m, 4 H), 1.62 (m, 2 H), 1.44 (m, 1 H), 1.37 (m, 3 H), 1.33 (s, 9 H), 1.24 (m, 2 H), 1.07 (m, 2 H), 1.03 (s, 9 H), LC-MS C (retention time: 2.81 ; MS m/z 831 (M+H).



Compound 92

Compound 92

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Trifluoromethyl-2-(4-trifluoromethyl-piperidin-1-yl)-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 8%): ^{1}H NMR (MeOH) δ 8.28 (s, 1 H), 7.32 (s, 2 H), 6.57 (d, J=8.9 Hz, 1 H), 5.79 (m, 1 H), 5.42 (s, 1 H), 5.27 (dd, J=1.2 Hz, 17.4 Hz, 1 H), 5.07 (d, J=10.1 Hz, 1 H), 4.45 (dd, J=7.6 Hz, 9.8 Hz, 1 H), 4.30 (d, J=12.2 Hz, 1 H), 4.25 (d, J= 9.5 Hz, 1 H), 4.03 (m, 1 H), 3.13 (t, J=15.0 Hz, 2 H), 2.90 (m, 1 H), 2.80 (m, 1 H), 2.70 (t, J=11.3 Hz, 1 H), 2.47 (dd, J=7.3 Hz, 14.0 Hz, 1 H), 2.31 (m, 2 H), 2.16 (dd, J=8.9 Hz, 17.7 Hz, 1 H), 2.00 (s, 1 H), 1.98 (s, 1 H), 1.85 (dd, J=5.2 Hz, 7.2 Hz, 1 H), 1.79 (m, 2 H), 1.39 (m, 1 H), 1.31 (s, 9 H), 1.18 (m, 2 H), 1.03 (s, 9 H), 1.00 (m, 2 H). LC-MS C (retention time: 2.89 ; MS m/z 895 (M+H).

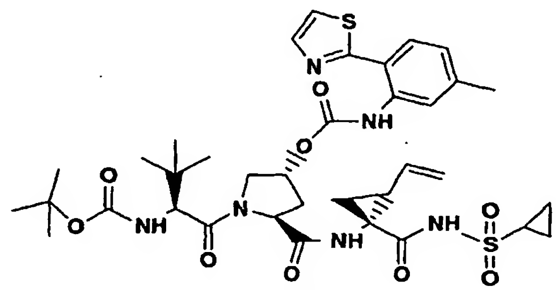


Compound 93

Compound 93

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-[1,2,3]Triazol-2-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 42%): ^{1}H NMR (MeOH) δ 8.24 (brs, 1 H), 7.99 (s, 2 H), 7.94 (d, J=7.9 Hz, 1 H), 7.40 (t, J=7.6 Hz, 1 H), 7.23 (t, J=7.6 xHz, 1 H), 6.61 (d, J=8.9, 1 H), 5.76 (m, 1 H), 5.39 (s, 1 H), 5.31 (d, J=17.1 Hz, 1 H), 5.13 (d, J=10.4 Hz, 1 H), 4.41 (m, 1 H), 4.25 (m, 2 H), 3.96 (dd,

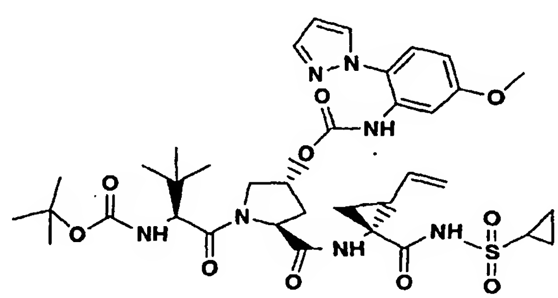
J=2.8 Hz, 11.6 Hz, 1 H), 2.94 (m, 1 H), 2.39 (m, 1 H), 2.24 (q, J=8.9 Hz, 1 H), 2.15 (m, 1 H), 1.87 (m, 1 H), 1.44 (m, 1 H), 1.29 (s, 9 H), 1.24 (m, 2 H), 1.07 (m, 2 H), 1.02 (s, 9 H). LC-MS C (retention time: 2.52 ; MS m/z 765 (M+Na).



Compound 94

Compound 94

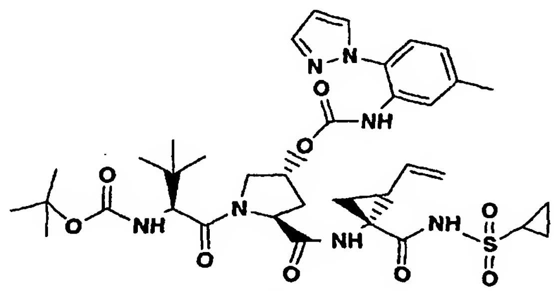
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Methyl-2-thiazol-2-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 76%): ^{1}H NMR (MeOH) δ 8.22 (s, 1 H), 7.83 (s, 1 H), 7.70 (d, J=7.6 Hz, 1 H), 7.55 (s, 1 H), 6.94 (d, J=7.6 Hz 1 H), 6.58 (d, J=8.2 Hz, 1 H), 5.77 (m, 1 H), 5.40 (s, 1 H), 5.29 (d, J=17.4 Hz, 1 H), 5.11 (d, J=10.4 Hz, 1 H), 4.46 (m, 1 H), 4.32 (d, J=11.3 Hz, 1 H), 4.25 (d, J=9.2 Hz, 1 H), 4.00 (d, J=10.7 Hz, 1 H), 2.93 (m, 1 H), 2.44 (m, 1 H), 2.37 (s, 3 H), 2.23 (m, 2 H), 1.87 (dd, J=5.5 Hz, 7.6 Hz, 1 H), 1.44 (m, 1 H), 1.23 (s, 11 H), 1.02 (s, 11 H). LC-MS C (retention time: 2.75 ; MS m/z 773 (M+H).



Compound 95

Compound 95

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Methoxy-2-pyrazol-1-yl-phenyl)))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 22%): ^{1}H NMR (MeOH) δ 7.92 (s, 1 H), 7.72 (s, 2 H), 7.33 (d, J=8.9 Hz, 1 H), 6.76 (d, J=7.9 Hz, 1 H), 6.62 (d, J=8.6 Hz, 1 H), 6.51 (s, 1 H), 5.76 (m, 1 H), 5.35 (s, 1 H), 5.31 (d, J=17.4 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.35 (m, 1 H), 4.23 (m, 2 H), 3.96 (m, 1 H), 3.84 (s, 3 H), 2.93 (m, 1 H), 2.36 (m, 1 H), 2.24 (m, 1 H), 2.15 (m, 1 H), 1.86 (m, 1 H), 1.44 (m, 1 H), 1.35 (s, 9 H), 1.24 (m, 2 H), 1.07 (d, J=7.3 Hz, 2 H), 1.01 (s, 9 H). LC-MS C (retention time: 2.43 ; MS m/z 772 (M+H).

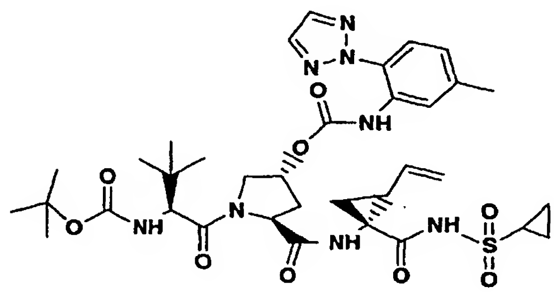


Compound 96

Compound 96

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Methyl-2-pyrazol-1-yl-phenyl)))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 13%): ^{1}H NMR (MeOH) δ 7.97 (d, J=1.8 Hz, 1 H), 7.91 (brs, 1 H), 7.74 (d, J=1.5 Hz, 1 H), 7.31 (d, J=8.2 Hz, 1 H), 7.03 (d, J=8.2 Hz, 1 H), 6.60 (d, J=9.2 Hz, 1 H), 6.51 (t, J=2.1 Hz, 1 H), 5.77 (m, 1 H), 5.33 (s, 1 H), 5.29 (dd, J=1.5 Hz, 17.1 Hz, 1 H), 5.11 (dd, J=1.5 Hz, 10.4 Hz, 1 H), 4.36 (dd, J=7.6 Hz, 9.8 Hz, 1 H), 4.24 (d, J=9.5 Hz, 1 H), 4.20 (d, J=12.2 Hz, 1 H), 3.95 (dd, J=3.1 Hz, 11.6 Hz, 1 H), 2.92 (m, 1 H), 2.38 (s, 3 H), 2.35

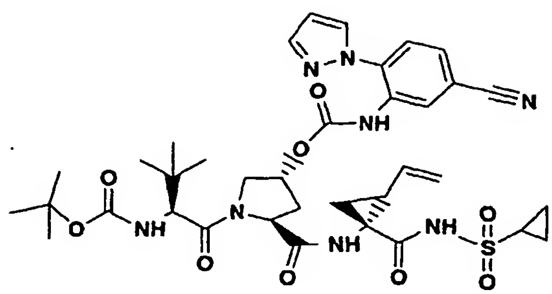
(m, 1 H), 2.20 (m, 2 H), 1.86 (dd, J=5.5 Hz, 7.9 Hz, 1 H), 1.44 (m, 1 H), 1.34 (s, 9 H), 1.22 (m, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS C (retention time: 2.49 ; MS m/z 756 (M+H).



Compound 97

Compound 97

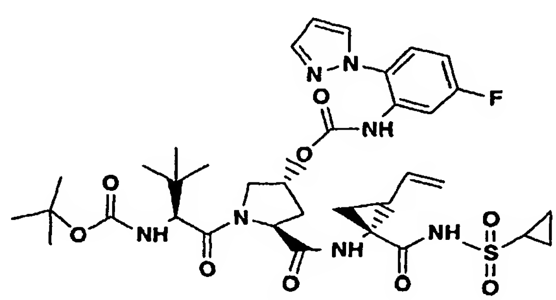
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 50%): ^{1}H NMR (MeOH) δ 8.05 (brs, 1 H), 7.96 (s, 2 H), 7.80 (d, J=8.2 Hz, 1 H), 7.05 (d, J=8.2 Hz, 1 H), 6.60 (d, J=9.5 Hz, 1 H), 5.76 (m, 1 H), 5.37 (s, 1 H), 5.30 (dd, J=1.5 Hz, 17.1 Hz, 1 H), 5.12 (dd, J=1.5 Hz, 10.1 Hz, 1 H), 4.40 (m, 1 H), 4.25 (m, 2 H), 3.96 (dd, J=3.1 Hz, 11.9 Hz, 1 H), 2.93 (m, 1 H), 2.40 (m, 4 H), 2.20 (m, 2 H), 1.87 (dd, J=5.5 Hz, 8.2 Hz, 1 H), 1.43 (m, 1 H), 1.29 (s, 9 H), 1.24 (m, 2 H), 1.07 (m, 2 H), 1.02 (s, 9 H). LC-MS C (retention time: 2.59 ; MS m/z 657 (M-Boc+H).



Compound 98

Compound 98

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Cyano-2-pyrazol-1-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 34%): ^{1}H NMR (MeOH) δ 8.63 (s, 1 H), 8.24 (s, 1 H), 7.84 (s, 1 H), 7.70 (d, J=8.2 Hz, 1 H), 7.54 (d, J=7.6 Hz, 1 H), 6.62 (m, 2 H), 5.76 (m, 1 H), 5.39 (s, 1 H), 5.31 (d, 17.1 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.40 (m, 1 H), 4.31 (d, J=11.6 Hz, 1 H), 4.23 (d, J=9.2 Hz, 1 H), 3.96 (d, J=9.5 Hz, 1 H), 2.93 (m, 1 H), 2.41 (m, 1 H), 2.22 (m, 2 H), 1.87 (dd, J=5.5 Hz, 7.9 Hz, 1 H), 1.43 (m, 1 H), 1.29 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.02 (s, 9 H). LC-MS C (retention time: 2.39 ; MS m/z 789 (M+Na).

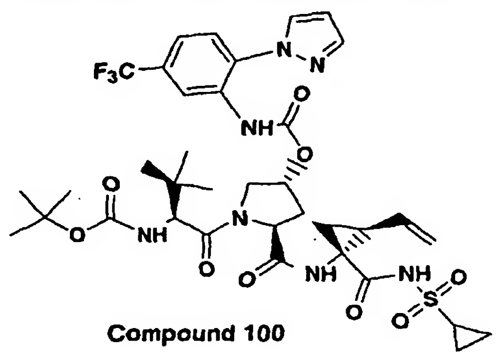


Compound 99

Compound 99

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-Fluoro-2-pyrazol-1-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane (Method B, 12%): ^{1}H NMR (MeOH) δ 8.02 (s, 2 H), 7.76 (s, 1 H), 7.46 (m, 1 H), 6.94 (m, 1 H), 6.61 (d, J=7.6 Hz, 1 H), 6.54 (s, 1 H), 5.76 (m, 1 H), 5.38 (s, 1 H), 5.30 (d, J=17.4 Hz, 1 H), 5.12 (d, J=10.4 Hz, 1 H), 4.37 (m, 1 H), 4.24 (m, 2 H), 3.97 (m, 1 H), 2.92 (m, 1 H), 2.38 (m, 1 H), 2.20 (m, 2 H), 1.86 (m, 1 H), 1.44 (m, 1 H), 1.32 (s, 9 H), 1.23 (m, 2 H), 1.06 (m, 2 H), 1.01 (s, 9 H). LC-MS C (retention time: 2.50 ; MS m/z 760 (M+H).

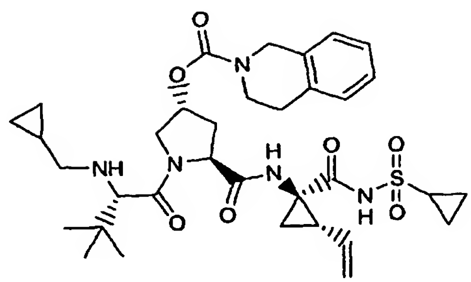
BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-trifluoromethyl-2-pyrazol-1-yl-phenyl))))-P1(1R,2S VinylAcca)-CONHSO2Cyclopropane



Compound 100

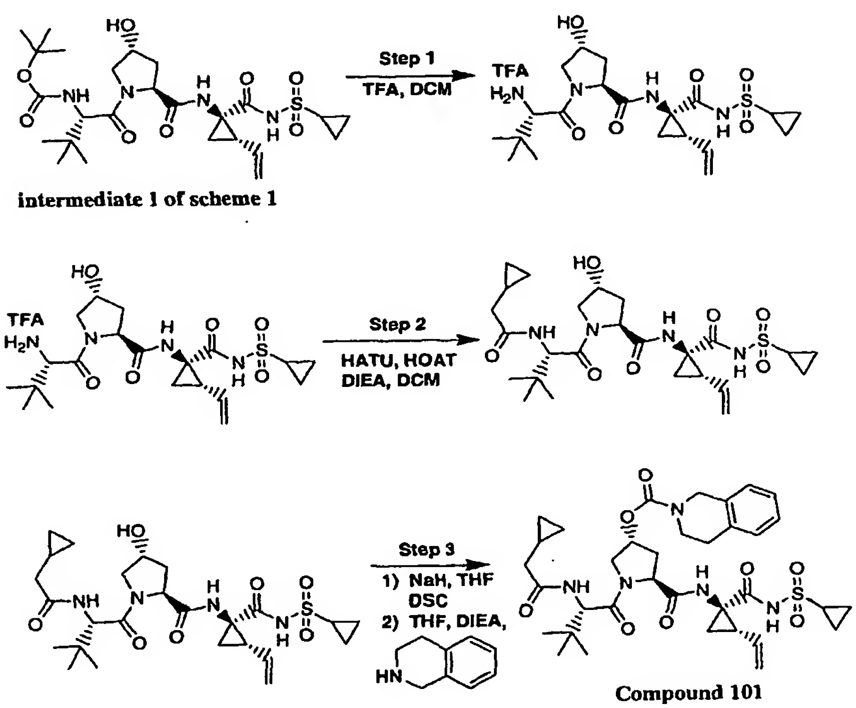
BMS-593177 (29%): ^{1}H NMR (MeOH) δ 8.62 (s, 1 H), 8.21 (s, 1 H), 7.83 (s, 1 H), 7.69 (d, J=8.2 Hz, 1 H), 7.48 (d, J=7.6 Hz, 1 H), 6.60 (s, 1 H), 5.77 (m, 1 H), 5.38 (s, 1 H), 5.29 (d, J=17.1 Hz, 1 H), 5.11 (d, J=10.4, 1 H), 4.40 (m, 1 H), 4.31 (d, J=12.2, 1 H), 4.23 (d, J=9.2, 1 H), 3.97 (d, J=10.4, 1 H), 2.93 (m, 1 H), 2.41 (m, 1 H), 2.21 (m, 2 H), 1.87 (m, 1 H), 1.44 (s, 1 H), 1.39 (s, 9 H), 1.16 (t, J=7.0 Hz, 2 H), 1.02 (m, 11 H); MS m/z 810 (M+H).

Preparation of Compound 101



Compound 101

Scheme 1 of Example 8: Preparation of compound 101



Step 1:

Intermediate 1 of scheme 1 (1.51 g, 2.71 mmol) was dissolved in a mixture of TFA (50 mL) and DCM (50 mL) and the resulting solution was stirred at rt for 30 min. The mixture was concentrated in vacuo and placed under high vacuum overnight. The desired product was obtained quantitatively and was used directly in the next step without purification: MS m/z 457 (M+H).

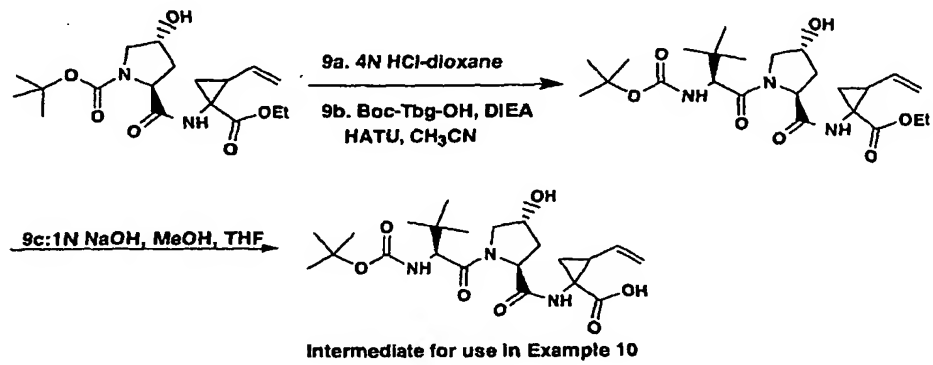
Step 2:

The product from step 1 (1.54 g, 2.71 mmol) was combined with DIEA (1.75 g, 13.6 mmol), cyclopropylacetic acid (0.363 g, 3.52 mmol) and DCM (25 mL). The mixture was treated with HATU (1.34 g, 3.52 mmol) and HOAT (0.479 g, 3.52 mmol) and the resulting solution was stirred at rt for 8 h. The mixture was diluted with DCM (50 mL) and washed with water (2 x 25 mL). The aqueous washes were back-extracted with DCM (2 x 50 mL), and the combined organic phases were washed with brine and dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a viscous oil. Purification by silica gel flash chromatography (30:1 DCM : MeOH) gave the desired product as a white solid: MS m/z 539 (M+H).

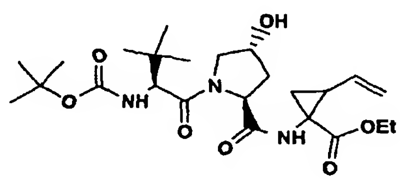
Step 3:

The product from Step 2 (50 mg, 0.093 mmol) was dissolved in THF (1 mL) and the solution was treated with NaH (60% oil dispersion, 12 mg, 0.28 mmol). The mixture was stirred for 5 min at rt, then DSC (80 mg, 0.28 mmol) was added and the resulting mixture was heated to 70 °C for 18h. The mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The aqueous wash was extracted with ethyl acetate four more times. The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to a white waxy solid. This crude material was redissolved in THF (1 mL) and the mixture was treated with 1,2,3,4-tetrahydroisoquinoline (37 mg, 0.28 mmol) and PS-DIEA (73 mg, 0.28 mmol). The resulting mixture was stirred for 72h and then treated with 4M HCl in 1,4-dioxane (1 mL) and MeOH (2 mL) and filtered to remove solids. The filtrate was concentrated in vacuo and purified by reverse phase preparative HPLC to give **Compound 101** as a yellow solid (24 mg, 37% yield): ^{1}H NMR (CD_3OD) δ 0.15 (s, 2 H), 0.47 (s, 2 H), 0.92-0.98 (m, 1 H), 1.05 (s, 9 H), 1.08-1.09 (m, 1 H), 1.22-1.26 (m, 2 H), 1.43 (dd, *J*=9.46, 5.49 Hz, 1 H), 1.87 (dd, *J*=8.24, 5.49 Hz, 1 H), 2.05-2.26 (m, 5 H), 2.39 (dd, *J*=13.28, 7.17 Hz, 1 H), 2.83 (s, 2 H), 2.91-2.95 (m, 1 H), 3.62-3.66 (m, 2 H), 3.95 (dd, *J*=11.90, 3.66 Hz, 1 H), 4.21 (d, *J*=11.60 Hz, 1 H), 4.38-4.42 (m, 1 H), 4.55-4.61 (m, 3 H), 5.13 (dd, *J*=10.38, 1.22 Hz, 1 H), 5.30 (dd, *J*=16.79, 0.92 Hz, 1 H), 5.36 (s, 1 H), 5.76 (ddd, *J*=17.32, 9.99, 9.31 Hz, 1 H), 7.15 (s, 4 H); MS m/z 698 (M+H).

Example 9: Preparation of BocNH-P3(t-BuGly)-P2(Hyp)-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2H, an intermediate for the preparation of tripeptide P2 carbamates, P1 carboxylic acids of Example 10:



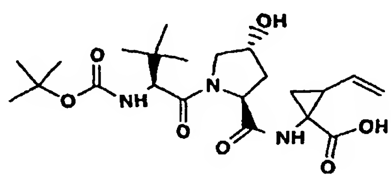
Step 9a and 9b: Preparation of BocNH-P3(t-BuGly)-P2(Hyp)-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2Et shown below:



BocNH-P2(Hyp)-P1((1*R*,2*S*)/(1S/2R) VinylAcca)-OEt (5.218g) was dissolved in 4N HCl dioxane. The resulting solution was stirred for 90 minutes and then concentrated *in vacuo* to yield a yellow foam which was taken on to the next step without further purification. The HCl salt of P2(Hyp)-P1((1*R*/2*S*)/(1S,2R) VinylAcca)-CO_2Et and N-Boc-*L*-tert-leucine (3.60g, 15.6 mmol) and 1.5 mL diisopropylethylamine were then dissolved in anhydrous acetonitrile (500 mL) under an atmosphere of nitrogen. The resulting solution was cooled to 0°C in an ice/ water bath. More diisopropylethylamine (7.13 mL, 41 mmol) was added to the solution followed by HATU (7.0g, 18.4 mmol). The reaction was stirred for 31 hours and then concentrated *in vacuo*. The residue was diluted with ethyl acetate (500 mL) and washed sequentially with 1N hydrochloric acid (500 mL), 1N sodium bicarbonate

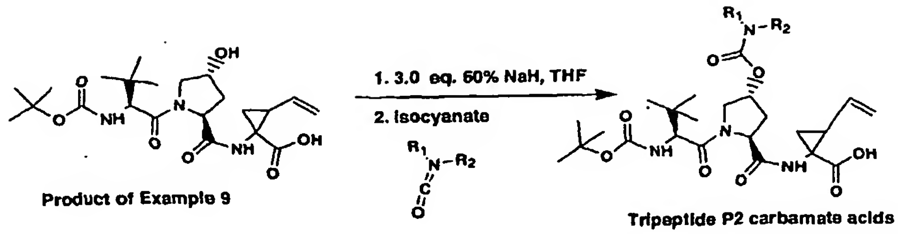
(500 mL) and brine (500 mL). The organic layer was dried over sodium sulfate and filtered through silica. The solution was concentrated and then purified via. silica flash chromatography eluting with 2:1 ethyl acetate: hexanes to yield 3.22g (32%) of the titled product as a white solid: ^{1}H NMR (d_4-MeOH, 500Mz) δ 5.73 (m, 1 H), 5.28 (m, 1H), 5.08 (app. t, J=10 Hz, 1H), 4.47 (m, 2H), 4.26 (m, 1H), 4.07-4.17 (m, 2H), 3.80 (m, 2H), 2.33 (m, 1H), 2.16-2.23 (m, 2H), 2.09 (m, 1H), 1.67-1.79 (m, 1H), 1.43 (s, 9H), 1.22 (t, J= 6.85 Hz, 3H), 1.02 and 1.00 (diastereotopic, 2s, 9H). LC-MS D (retention time: 1.65 ; MS m/z 482 (M+H).

Step 9c: Preparation of BocNH-P3(t-BuGly)-P2(Hyp)-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2H shown below:



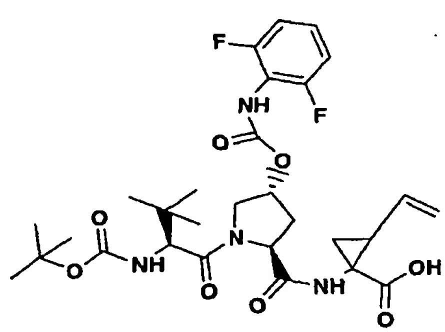
BocNH-P3(t-BuGly)-P2(Hyp)-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2Et (2.705g, 5.62 mmol) was dissolved in methanol (18 mL) and tetrahydrofuran (50mL). The solution was cooled to 2°C in an ice/ water bath. 1N NaOH (16.9 mL) was then added to the cooled solution. After stirring for three hours, the solution was concentrated to ~20 mL and 0.5N sodium bicarbonate (60 mL) and ethyl acetate (60 mL) were added. The layers were separated and then the basic aqueous layer was acidified to pH 1 with 1N hydrochloric acid. The acidified aqueous phase was then extracted with ethyl acetate (3x100 mL) and these organics were dried with sodium sulfate and concentrated *in vacuo* to yield 2.11g (83%) of the titled compound as a white powder which was taken on to the next step without further purification.

Example 10: General procedure for the preparation of tripeptide P2 – carbamate P1 acids (Compounds 102-109), as shown below in general form, from the intermediate prepared in Example 9:



Representative procedure to make tripeptide P2-carbamate P1 acids (BocNH-P3(t-BuGly)-P2(Hyp(O-CO-NR^{1}R^2)-P1((*1R,2S*)/(*1S,2R*) VinylAcca)-CO_2H) using isocyanates :

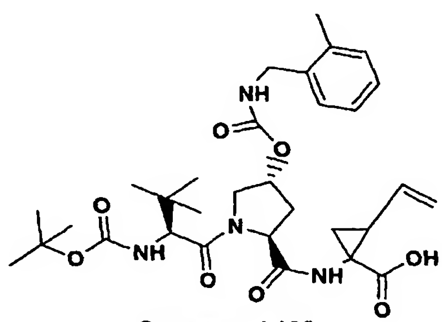
BocNH-P3(t-BuGly)-P2(Hyp)-P1((1*R*,2*S*)/(1S,2R) VinylAcca)-CO_2H (150 mgs, 0.33 mmol) was dissolved in tetrahydrofuran (1.6 mL). The resulting solution was cooled in an CH_3CN/ CO_2 bath to –39°C. 60% NaH (40 mgs, 0.99 mmol) was added to the reaction followed by slow addition of the desired isocyanate (0.38 mmol) over 30 minutes. The sides of the flask were then washed with tetrahydrofuran (500□L) and the reaction was left to warm up in the cold bath overnight. After stirring for 22 hours, the reaction was quenched with 0.5N sodium bicarbonate (10 mL). Ethyl acetate (20 mL) and 0.5N sodium bicarbonate (20 mL) were added and the layers separated. The basic aqueous layer was acidified with 1N hydrochloric acid until pH 1 and then extracted with ethyl acetate (2x30 mL). These ethyl acetate layers were dried with sodium sulfate, filtered and concentrated *in vacuo* to yield the following tripeptide P2-carbamate acids:



Compound 102

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2,6-difluoro-phenyl))))-P1((*1R,2S*)/(*1S,2R*) VinylAcca)-CO_2H:

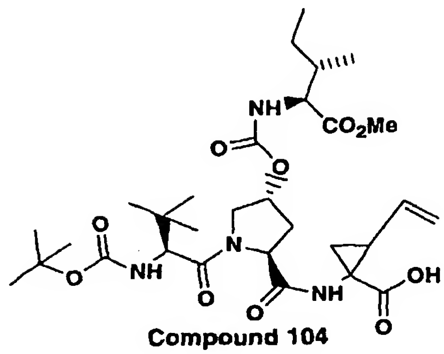
(57%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.27 (m, 1H), 7.00 (m, 2H), 6.00 (m, 1H), 5.37 (d, J=13.4 Hz), 1H), 5.21 (dd, J=17.4 and 17.1 Hz, 1H), 4.99 (dd, J=10.7 and 10.1 Hz, 1H), 4.50-4.57 (m, 1H), 4.32 (m, 1H), 4.09 (m, 1H), 3.94 (m, 1H), 2.43 (m, 1H), 2.18-2.29 (m, 1H), 1.96-2.11 (m, 1H), 1.56-1.69 (m, 1H), 1.44 and 1.43 (diastereotopic, 2s, 9H), 1.28 (m, 1H), 0.99 and 0.98 (diastereotopic, 2s, 9H). LC-MS D (retention time: 1.63 ; MS m/z 609 (M+H).



Compound 103

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-methyl-benzyl))))-P1((*1R,2S*)/(*1S,2R*) VinylAcca)-CO_2H:

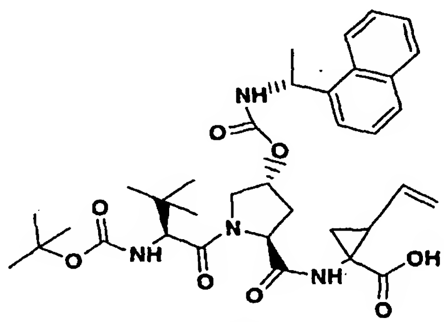
(48%): ^{1}H NMR (d_4-MeOH, 500Mz) δ 7.20 (m, 1H), 7.12 (m, 3H), 5.97 (m, 1H), 5.28 (m, 1H), 5.21 (dd, J=17.7 and 17.1 Hz, 1H), 4.97 (dd, J=11.3 and 11.0 Hz, 1H), 4.47 (m, 1H), 4.21-4.31 (m, 3H), 4.01 (m, 1H), 3.89 (m, 1H), 2.25-2.40 (m, 1H), 2.29 (s, 3H), 2.07-2.16 (m, 1H), 1.97 (m, 1H), 1.51-1.69 (m, 1H), 1.43 and 1.42 (diastereotopic, 2s, 9H), 1.28 (m, 1H), 0.99 and 0.98 (diastereotopic, 2s, 9H). LC-MS D (retention time: 1.77 ; MS m/z 601 (M+H).



Compound 104

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-2-[(2S,3S)-3-methyl valeric acid methyl ester])))-P1((*1R,2S)/(1S,2R)* VinylAcca)-CO_2H:

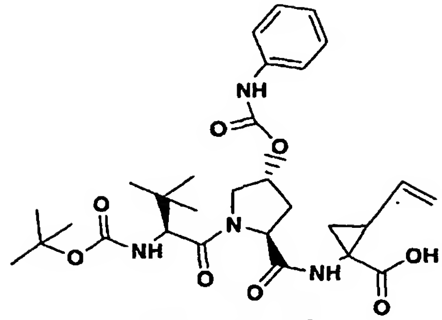
(59%): LC-MS D (retention time: 1.76 ; MS m/z 625 (M+H).



Compound 105

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-1-(R)-1-naphthyl ethyl)))-P1((*1R,2S)/(1S,2R)* VinylAcca)-CO_2H:

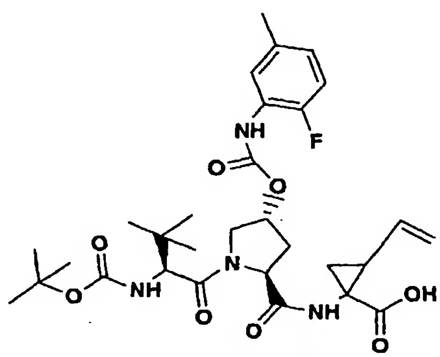
(9%): LC-MS D (retention time: 1.87 ; MS m/z 651 (M+H).



Compound 106

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-phenyl)))-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2H:

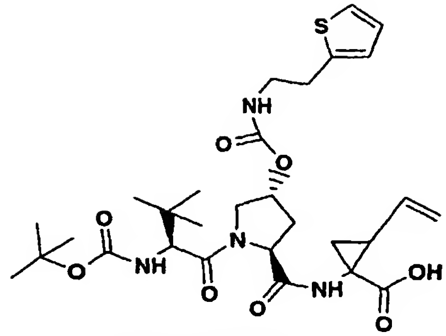
(42%): LC-MS D (retention time: 1.72 ; MS m/z 573 (M+H).



Compound 107

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(5-methyl-2-fluoro-phenyl)))-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2H:

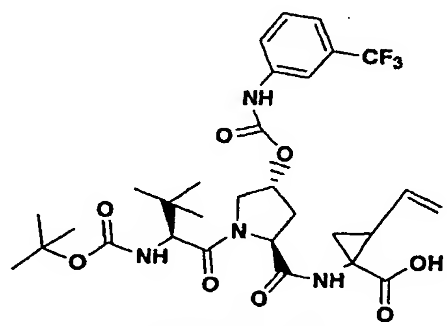
(25%): LC-MS D (retention time: 1.78 ; MS m/z 605 (M+H).



Compound 108

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(2-thiophen-2-yl-ethyl))))-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2H:

(50%): LC-MS D (retention time: 1.73 ; MS m/z 607 (M+H).



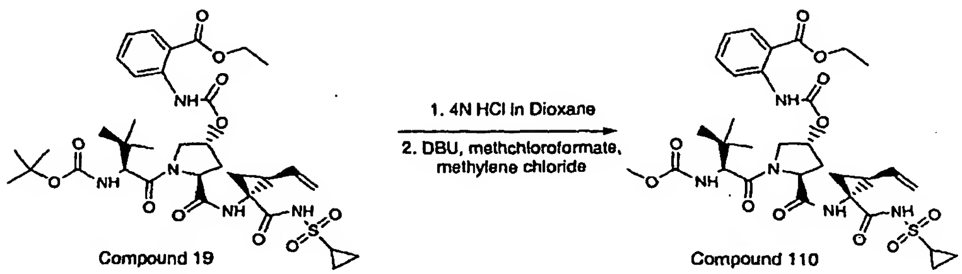
Compound 109

BocNH-P3(t-BuGly)-P2(Hyp(O-CO(NH-(3-trifluoromethyl-phenyl))))-P1((1*R*,2*S*)/(1*S*,2*R*) VinylAcca)-CO_2H:

(18%): LC-MS D (retention time: 1.87 ; MS m/z 641 (M+H).

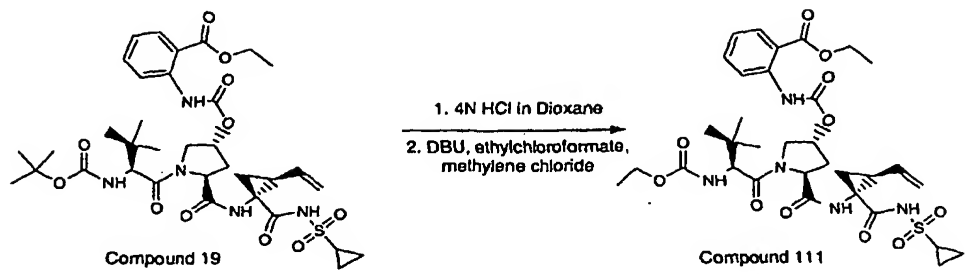
Example 11

Compounds 110 and 111 were prepared from Compound 19 using the chemistry described in the present example.



Compound 19 (88 mg, 0.12 mmole) dissolved in 4N HCl in dioxane (0.29mL, 1.20 mmmole). After stirring at 25C for 1 hour, diethyl ether (10 mL) added, and solvent removed in vacuo yielding the de-blocked HCl salt, which was taken to the next step without further purification.

The HCl salt of the desboc analogue of Compound 19 (0.12 mmol) was dissolved in methylene chloride (6 mL). 4,8-diazabicyclo[5.4.0]non-5-ene (356mg, 0.24 mmol) added to the solution, followed immediately by methylchloroformate (11mg, .12 mmol). The yellow mixture was stirred at 25C for 18 hours. The reaction was diluted with ethyl acetate (50 mL) and 1N HCl (50 mL). The organic portion was separated, and washed with 1N HCl (1 x 50 mL), and brine (1 x 50 mL). The organic portion was dried over sodium sulfate and concentrated *in vacuo*. The product was purified by Prep TLC eluting with 1:1 ethyl acetate: hexanes to compound 110 (67%).



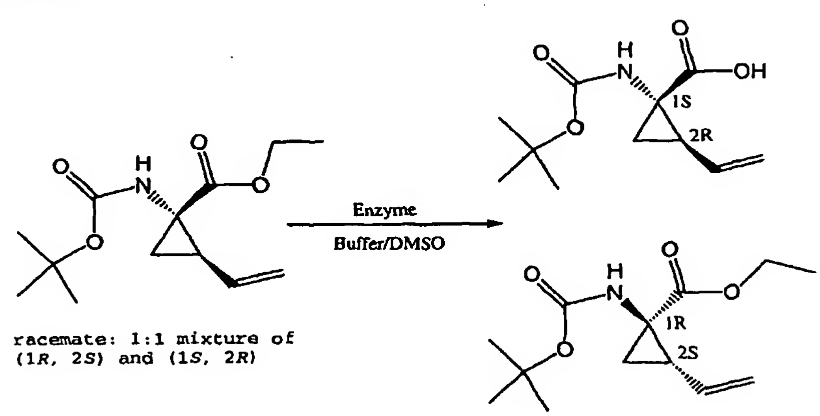
Compound 111 was prepared from Compound 19 using procedure shown above for the preparation of Compound 110 except that ethylchloroformate was used in place of methylchloroformate.

Example12

Section 1 of Example 12:

Preparation of P1 Elements: The following additional P1 and P1` elements were prepared as described below.

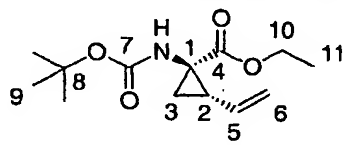
1. Resolution of N-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester



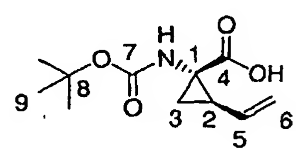
Resolution A

To an aqueous solution of sodium phosphate buffer (0.1 M, 4.25 liter ("L"), pH 8) housed in a 12 Liter jacked reactor, maintained at 39°C, and stirred at 300 rpm was added 511 grams of Acalase 2.4L (about 425 mL) (Novozymes North America Inc.). When the temperature of the mixture reached 39°C, the pH was adjusted to 8.0 by the addition of a 50% NaOH in water. A solution of the racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (85g) in 850 mL of DMSO was then added over a period of 40 min. The reaction temperature was then maintained at 40°C for 24.5h during which time the pH of the mixture was adjusted to 8.0 at the 1.5h and 19.5h time points using 50% NaOH in water. After 24.5h, the enantio-excess of the ester was determined to be 97.2%, and the reaction was cooled to room temperature (26°C) and stirred overnight (16h) after which the enantio-excess of the ester was determined to be 100%. The pH of the reaction mixture was then adjusted to 8.5 with 50% NaOH and the resulting mixture was extracted with MTBE (2 x 2 L). The combined MTBE extract was then washed with 5% $NaHCO_3$ (3 x 100 mL), water (3 x 100 mL), and evaporated *in vacuo* to give the enantiomerically pure *N*-Boc-(1*R*,2*S*)/-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as light yellow solid (42.55 g; purity: 97% @ 210 nm, containing no acid; 100% enantiomeric excess ("ee").

The aqueous layer from the extraction process was then acidified to pH 2 with 50% H_2SO_4 and extracted with MTBE (2 x 2 L). The MTBE extract was washed with water (3 x 100 mL) and evaporated to give the acid as light yellow solid (42.74 g; purity: 99% @ 210 nm, containing no ester).



1R, 2S-ester



1S,2R-acid

	ester	acid
High Resolution Mass Spec	(+) ESI, C13H22NO4, $[M+H]^+$, cal. 256.1549, found 256.1542	(-) ESI, C11H16NO4, $[M-H]^-$, cal. 226.1079, found 226.1089

NMR observed chemical shift

Solvent: $CDCl_3$ (proton δ 7.24 ppm, C-13 δ 77.0 ppm)

Bruker DRX-500C: proton 500.032 MHz, carbon 125.746 MHz

Position	Proton (pattern) ppm	C-13 ppm	Proton (pattern) ppm	C-13 ppm
1	----	40.9	----	40.7
2	2.10 (q, J = 9.0 Hz)	34.1	2.17 (q, J = 9.0 Hz)	35.0
3a	1.76 (br)	23.2	1.79 (br)	23.4
3b	1.46 (br)		1.51, (br)	
4	----	170.8	----	175.8
5	5.74 (ddd, J = 9.0, 10.0, 17.0 Hz)	133.7	5.75 (m)	133.4
6a	5.25 (d, J = 17.0 Hz)	117.6	5.28 (d, J = 17.0 Hz)	118.1
6b	5.08 (dd, J = 10.0, 1.5 Hz)		5.12 (d, J = 10.5 Hz)	
7	----	155.8	----	156.2
8	----	80.0	----	80.6
9	1.43 (s)	28.3	1.43 (s)	28.3
10	4.16 (m)	61.3	----	----
11	1.23 (t, J = 7.5 Hz)	14.2	----	----

Resolution B

To 0.5 mL 100 mM Heps•Na buffer (pH 8.5) in a well of a 24 well plate (capacity: 10 ml/well), 0.1 mL of Savinase 16.0L (protease from *Bacillus clausii*) (Novozymes North America Inc.) and a solution of the racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (10 mg) in 0.1 mL of DMSO were added. The plate was sealed and incubated at 250 rpm at 40°C. After 18h, enantio-excess of the ester was determined to be 44.3% as following: 0.1 mL of the reaction mixture was removed and mixed well with 1 mL ethanol; after centrifugation, 10 microliter ("μl") of the supernatant was analyzed with the chiral HPLC. To the remaining reaction mixture, 0.1 mL of DMSO was added, and the plate was incubated for additional 3 days at 250 rpm at 40°C, after which four mL of ethanol was added to the well. After centrifugation, 10 μl of the supernatant was analyzed with the chiral HPLC and enantio-excess of the ester was determined to be 100%.

Resolution C

To 0.5 ml 100 mM Heps•Na buffer (pH 8.5) in a well of a 24 well plate (capacity: 10 mL/well), 0.1 ml of Esperase 8.0L, (protease from *Bacillus halodurans*) (Novozymes North America Inc.) and a solution of the racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (10 mg) in 0.1 mL of DMSO were added. The plate was sealed and incubated at 250 rpm at 40°C. After 18 hour, enantio-excess of the ester was determined to be 39.6% as following: 0.1 mL of the reaction mixture was removed and mixed well with 1 mL ethanol; after cenrifugation, 10 μl of the supernatant was analyzed with the chiral HPLC. To the remaining reaction mixture, 0.1 mL of DMSO was added, and the plate was incubated for additional 3 days at 250 rpm at 40°C, after which four mL of ethanol was added to the well. After centrifugation, 10 μl of the supernatant was analyzed with the chiral HPLC and enantio-excess of the ester was determined to be 100%.

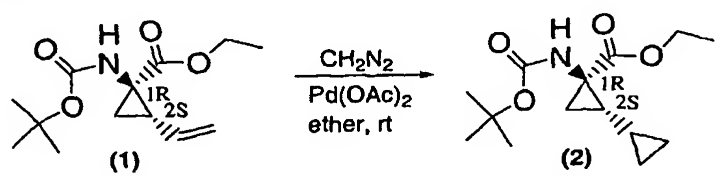
Samples analysis was carried out in the following manner:

1) Sample preparation: About 0.5 ml of the reaction mixture was mixed well with 10 volume of EtOH. After centrifugation, 10 μl of the supernatant was injected onto HPLC column.

2) Conversion determination:
Column: YMC ODS A, 4.6 x 50 mm, S-5 μm
Solvent: A, 1 mM HCl in water; B, MeCN
Gradient: 30% B for 1 min; 30% to 45% B over 0.5 min; 45% B for 1.5 min; 45% to 30% B over 0.5 min.
Flow rate: 2 ml/min
UV Detection: 210 nm
Retention time: acid, 1.2 min; ester, 2.8 min.

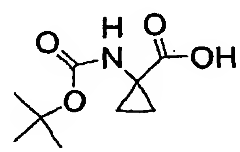
3) Enantio-excess determination for the ester:
Column: CHIRACEL OD-RH, 4.6 x 150 mm, S-5 μm
Mobile phase: MeCN/50 mM $HClO_4$ in water (67/33)
Flow rate: 0.75 ml/min.
UV Detection: 210 nm.
Retention time:
(1S, 2R) isomer as acid: 5.2 min;
Rcaemate: 18.5 min and 20.0 min;
(1R, 2S) isomer as ester: 18.5 min.

2. Preparation of *N*-Boc-(1*R*,2*S*)-1-amino-2-cyclopropylcyclopropane carboxylic acid ethyl ester

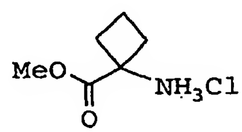


A solution of *N*-Boc-(1*R*,2*S*)-1-amino-2-vinylcyclopropane carboxylic acid (255 mg, 1.0 mmol) in ether (10 mL) was treated with palladium acetate (5 mg, 0.022 mmol). The orange/red solution was placed under an atmosphere of N_2. An excess of diazomethane in ether was added dropwise over the course of 1 h. The resulting solution was stirred at rt for 18 h. The excess diazomethane was removed using a stream of nitrogen. The resulting solution was concentrated by rotary evaporation to give the crude product. Flash chromatography (10% EtOAc/hexane) provided 210 mg (78%) of *N*-Boc-(1*R*,2*S*)-1-amino-2-cyclopropylcyclopropane carboxylic acid ethyl ester as a colorless oil. LC-MS (retention time: 2.13, similar to method A except: gradient time 3 min, Xterra MS C18 S7 3.0 x 50mm column), MS m/e 270 (M^++1).

3. 1-tert-butoxycarbonylamino-cyclopropane-carboxylic acid is commercially available

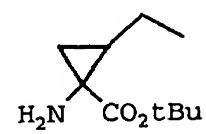


4. Preparation of 1-aminocyclobutanecarboxylic acid methyl ester·hydrochloride



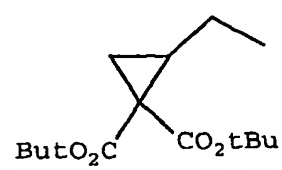
1-aminocyclobutanecarboxylic acid (100 mg, 0.869 mmol)(Tocris) was dissolved in 10 mL of MeOH, HCl gas was bubbled in for 2h. The reaction mixture was stirred for 18 h, and then concentrated in vacuo to give 144 mg of a yellow oil. Trituration with 10 mL of ether provided 100 mg of the titled product as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.10-2.25 (m, 1H), 2.28-2.42 (m, 1H), 2.64-2.82 (m, 4H), 3.87 (s, 3H), 9.21 (br s, 3H).

5. Preparation of racemic (1*R*,2*R*)/(1*S*,2*S*) 1-Amino-2-ethylcyclopropanecarboxylic acid *tert*-butyl ester, shown below.



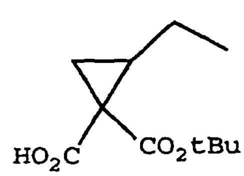
ethyl syn to carboxy

Step 1: Preparation of 2-Ethylcyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester, shown below.



To a suspension of benzyltriethylammonium chloride (21.0 g, 92.2 mmol) in a 50% aqueous NaOH solution (92.4 g in 185 mL H_2O) was added 1,2-dibromobutane (30.0 g, 138.9 mmol) and di-tert-butylmalonate (20.0 g, 92.5 mmol). The reaction mixture was vigorously stirred 18 h at rt, a mixture of ice and water was then added. The crude product was extracted with CH_2Cl_2 (3x) and sequentially washed with water (3x), brine and the organic extracts combined. The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting residue was flash chromatographed (100 g SiO_2, 3% Et_2O in hexane) to afford the titled product (18.3 g, 67.8 mmol, 73% yield) which was used directly in the next reaction.

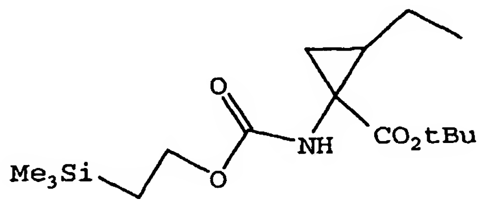
Step 2: Preparation of racemic 2-Ethylcyclopropane-1,1-dicarboxylic acid tert-butyl ester, shown below.



The product of Step 1 (18.3 g, 67.8 mmol) was added to a suspension of potassium tert-butoxide (33.55 g, 299.0 mmol) in dry ether (500 mL) at 0 °C, followed by H_20 (1.35 mL, 75.0 mmol) and was vigorously stirred overnight at rt. The reaction mixture was poured in a mixture of ice and water and washed with ether (3x). The aqueous layer was acidified with a 10% aq. citric acid solution at 0°C and extracted with EtOAc (3x). The combined organic layers were washed with water (2x), brine,

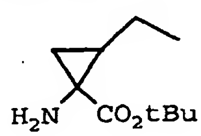
dried ($MgSO_4$) and concentrated in vacuo to afford the titled product as a pale yellow oil (10 g, 46.8 mmol, 69% yield).

Step 3: Preparation of (*1R,2R*)/(1*S*,2*S*) 2-Ethyl-1-(2-trimethylsilanylethoxycarbonylamino)cyclopropane-carboxylic acid tert-butyl ester, shown below.



To a suspension, of the product of Step 2 (10 g, 46.8 mmol) and 3 g of freshly activated 4A molecular sieves in dry benzene (160 mL), was added Et_3N (7.50 mL, 53.8 mmol) and DPPA (11 mL, 10.21 mmol). The reaction mixture was refluxed for 3.5 h, 2-trimethylsilyl-ethanol (13.5 mL, 94.2 mmol) was then added, and the reaction mixture was refluxed overnite. The reaction mixture was filtered, diluted with Et_2O, washed with a 10% aqueous citric acid solution, water, saturated aqueous $NaHCO_3$, water (2x), brine (2X), dried ($MgSO_4$) and concentrated in vacuo. The residue was suspended with 10g of Aldrich polyisocyanate scavenger resin in 120 mL of CH_2Cl_2, stirred at rt overnite and filtered to afford the titled product (8 g, 24.3 mmol; 52%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.97 (m, 5H), 1.20 (bm, 1H), 1.45 (s, 9H), 1.40-1.70 (m, 4H), 4.16 (m, 2H), 5.30 (bs, 1H).

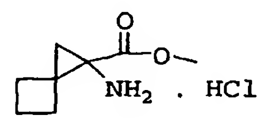
Step 4: Preparation of racemic (1*R*,2*R*)/(*1S*,2*S*) 1-Amino-2-ethylcyclopropanecarboxylic acid *tert*-butyl ester, shown below.



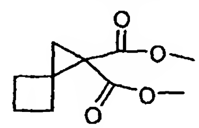
ethyl syn to carboxy

To the product of Step 3 (3 g, 9 mmol) was added a 1.0 M TBAF solution in THF (9.3 mL, 9.3 mmol) and the mixture heated to reflux for 1.5 h, cooled to rt and then diluted with 500 ml of EtOAc. The solution was successively washed with water (2x100 mL), brine (2x100 mL), dried ($MgSO_4$), concentrated in vacuo to provide the title intermediate

6.Preparation of 1-Amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt

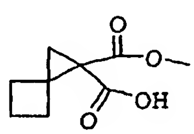


Step 1 Preparation of [2,3]hexane-1,1-dicarboxylic acid dimethyl ester, shown below.



To a mixture of methylene-cyclobutane (1.5 g, 22 mmol) and $Rh_2(OAc)_4$ (125 mg, 0.27 mmol) in anhydrous CH_2Cl_2 (15 mL) was added 3.2 g (20 mmol) of dimethyl diazomalonate (prepared according to J. Lee et al. *Synth. Comm.*, 1995, *25*, 1511-1515) at 0°C over a period of 6 h. The reaction mixture was then warmed to rt and stirred for another 2 h. The mixture was concentrated and purified by flash chromatography (eluting with 10:1 hexane/Et_2O to 5:1 hexane/Et_2O) to give 3.2 g (72%) of [2,3]hexane-1,1-dicarboxylic acid dimethyl ester as a yellow oil. ^1H NMR (300 MHz, CDCl3) δ 3.78 (s, 6 H), 2.36 (m, 2 H), 2.09 (m, 3 H), 1.90 (m, 1 H), 1.67 (s, 2 H). LC-MS: MS m/z 199 (M^++1).

Step 2: Preparation of spiro[2,3]hexane-1,1-dicarboxylic acid methyl ester, shown below.

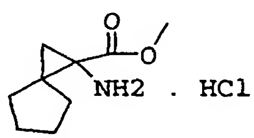


To the mixture of spiro [2,3]hexane-1,1-dicarboxylic acid dimethyl ester (200 mg, 1.0 mmol) in 2 mL of MeOH and 0.5 mL of water was added KOH (78 mg, 1.4 mmol). This solution was stirred at rt for 2 days. It was then acidified with dilute HCl and extracted two times with ether. The combined organic phases were dried ($MgSO_4$) and concentrated to yield 135 mg (73%) of 2 as a white solid. ^1H NMR (300 MHz, CDCl3) δ 3.78 (s, 3 H), 2.36-1.90 (m, 8 H). LC-MS: MS m/z 185 (M^++1)

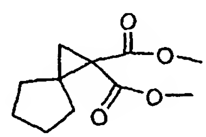
Step 3: Preparation of the titled product, 1-amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt.

To a mixture of spiro[2,3]hexane-1,1-dicarboxylic acid methyl ester (660 mg, 3.58 mmol) in 3 mL of anhydrous t-BuOH was added 1.08 g (3.92 mmol) of DPPA and 440 mg (4.35 mmol) of Et_3N. The mixture was heated at reflux for 21 h and then partitioned between H_2O and ether. The ether phase was dried over magnesium sulfate, filtered and concentrated in vacuo to yield an oil. To this oil was added 3 mL of a 4 M HCl/dioxane solution. This acidic solution was stirred at rt for 2 h and then concentrated in vacuo. The residue was triturated with ether to give 400 mg (58 %) of desried prodict as a white solid. ^1H NMR (300 MHz, d6-DMSO) δ 8.96 (br s, 3 H), 3.71 (s, 3 H), 2.41 (m, 1 H), 2.12 (m, 4 H), 1.93 (m, 1 H), 1.56 (q, 2 H, J=8 Hz). LC-MS of free amine: MS m/z 156 (M^++1).

7. Preparation of 1-Amino-spiro[2.4]heptane-1-carboxylic acid methyl ester hydrochloride salt, shown below, was prepared as follows.



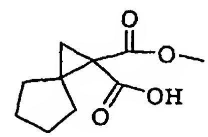
Step 1: Spiro[2.4]heptane-1,1-dicarboxylic acid dimethyl ester, shown below, was prepared as follows.



Using the same procedure described in the preparation of 1-Amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt

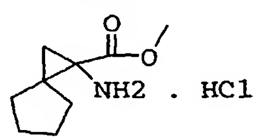
1.14g (13.9 mmol) of methylenecyclopentane and 2.0 g (12.6 mmol) of dimethyl diazomalonate were reacted to yield 1.8 g (67%) of the dimethyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6 H), 1.80 (m, 2 H), 1.70 (m, 4 H), 1.60 (m, 4 H). LC-MS: MS m/z 213 (M^++1).

Step 2: Preparation of Spiro[2.4]heptane-1,1-dicarboxylic acid methyl ester, shown below, was prepared as follows.



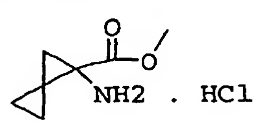
Using the same procedure described in the preparation of 1-Amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt
1.7 g (8.0 mmol) of the produc of Step 1 and 493 mg (8.8 mmol) of KOH gave 1.5 g (94%) of spiro[2.4]heptane-1,1-dicarboxylic acid methyl ester. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3 H), 2.06 (d, 1 H, *J*=5 Hz), 1.99 (d, 1 H, *J*=5 Hz), 1.80–1.66 (m, 8 H). LC-MS: MS m/z 199 (M^{+}+1).

Step 3: Preparation of 1-Amino-spiro[2.4]heptane-1-carboxylic acid methyl ester hydrochloride salt, shown below, was prepared as follows.

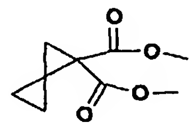


Using the same procedure described above in preparation of 1-Amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt, 500 mg (2.5 mmol) of the product of Step 2, 705 mg (2.5 mmol) of DPPA and 255 mg (2.5 mmol) of Et_3N gave 180 mg (35%) of this hydrochloride salt. ^{1}H NMR (300 MHz, d6-DMSO) δ 8.90 (br s, 3 H), 3.74 (s, 3 H), 1.84 (m, 1 H), 1.69 (m, 4 H), 1.58 (m, 4 H), 1.46 (d, 1 H, *J*=6 Hz). LC-MS of free amine: MS m/z 170 (M^{+}+1).

8. Preparation of 1-Amino-spiro[2.2]pentane-1-carboxylic acid methyl ester hydrochloride salt, shown below, was prepared as follows.

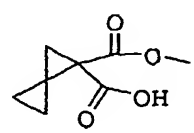


Step 1: Spiro[2.2]pentane-1,1-dicarboxylic acid dimethyl ester, shown below, was prepared as follows.



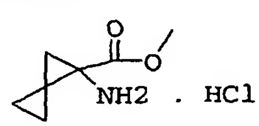
To a mixture of methylenecyclopropane (1.0 g, 18.5 mmol)(prepared according to P. Binger US Patent Serial No. 5,723,714) and $Rh_2(OAc)_4$ (82mg, 0.185 mmol) in anhydrous CH_2Cl_2 (10 mL), was added dimethyl diazomalonate (2.9 g, 18.3 mmol) at 0°C. At the top of the flask was installed a cold finger, the temperature of which was kept at –10°C. The reaction mixture was warmed to rt and stirred for another 2 h. The mixture was concentrated in vacuo and purified by flash chromatography (eluting with 10:1 hexane/Et_2O to 5:1 hexane/Et_2O) to give 0.85 g (25%) of the dimethyl ester as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6 H), 1.92 (s, 2 H), 1.04 (d, 4 H, J=3 Hz).

Step 2: Spiro[2.2]pentane-1,1-dicarboxylic acid methyl ester, shown below, was prepared as follows.



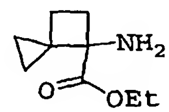
Using the same procedure described above in preparation of 1-Amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt, 800 mg (4.3 mmol) of the product of step 1 and 240 mg (4.3 mmol) of KOH gave 600 mg (82%) of Spiro[2.2]pentane-1,1-dicarboxylic acid methyl ester. ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 6 H), 2.35 (d, 1 H, J=3 Hz), 2.26 (d, 1 H, J=3 Hz), 1.20 (m, 1 H), 1.15 (m, 1 H), 1.11 (m, 1 H), 1.05 (m, 1 H). LRMS: MS m/z 169 (M^+-1) (Method D).

Step 3: 1-Amino-spiro[2.2]pentane-1-carboxylic acid methyl ester hydrochloride salt, shown below, was prepared as follows.



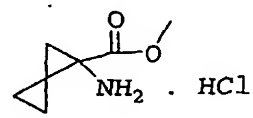
Using the same procedure described above for the preparation of 1-Amino-spiro[2.3]hexane-1-carboxylic acid methyl ester hydrochloride salt, 400 mg (2.3 mmol) of the product of step 2, 700 mg (2.5 mmol) of DPPA and 278 mg (2.7 mmol) of Et_3N gave 82 mg (20%) of the hydrochloride salt. ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (br s, 3 H), 3.81 (s, 3 H), 2.16, (d, J=5.5 Hz, 1 H), 2.01 (d, J=5.5 Hz, 1 H), 1.49 (m, 1 H), 1.24, (m, 1 H), 1.12 (m, 2 H). LRMS of free amine: MS m/z 142 (M^++1).

9. Preparation of 5-Amino-spiro[2.3]hexane-5-carboxylic acid ethyl ester, shown below, was prepared as follows.

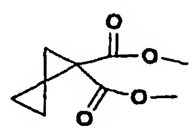


Spiro[2.3]hexan-4-one (500 mg, 5 mmol), which was prepared from bicyclopropylidene (A. Meijere et al. *Org. Syn.* 2000, *78*, 142-151) according to A. Meijere et al. *J. Org. Chem.* 1988, *53*, 152-161, was combined with ammonium carbamate (1.17 g, 15 mmol) and potassium cyanide (812 mg, 12.5 mmol) in 50 mL of EtOH and 50 mL of water. The mixture was heated at 55 °C for 2 days. Then NaOH (7 g, 175 mmol) was added and the solution was heated under reflux overnight. The mixture was then chilled to 0 °C, acidified to pH 1 with concentrated HCl, and concentrated in vacuo. EtOH was added to the crude amino acid mixture and then concentrated to dryness (5x) so as to remove residual water. The residue dissolved in 100 mL of EtOH was cooled to 0 °C. It was then treated with 1 mL of $SOCl_2$ and refluxed for 3 days. The solids were removed by filtration, and the filtrate was concentrated in vacuo to give the crude product. The crude product was partitioned between 3 N NaOH, NaCl and EtOAc. The organic phase was dried over potassium carbonate and concentrated. The residue was purified using column chromatography on C18 silica gel (eluting with MeOH/H_2O) to yield 180 mg (21%) of 15 as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (br s, 2 H), 4.27 (s, 2 H), 2.80 (s, 1 H), 2.54 (s, 1 H), 2.34 (m, 2 H), 1.31 (s, 3 H), 1.02 (s, 1 H), 0.66 (m, 3 H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.2(s), 63.0(s), 62.8 (s), 26.1 (s), 26.0 (s), 24.9 (s), 13.9 (s), 11.4 (s), 10.9 (s). LC-MS: MS m/z 170 (M^++1).

10. Preparation of 1-Amino-spiro[2.2]pentane-1-carboxylic acid methyl ester hydrochloride salt, shown below, was prepared as follows.

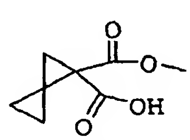


Step 1 Preparation of spiro[2.2]pentane-1,1-dicarboxylic acid dimethyl ester, shown below.



To a cooled (0°C) mixture of methylenecyclopropane (3.89 g, 72 mmol)(prepared according to P. Binger US Patent Serial No. 5,723,714) and $Rh_2(OAc)_4$ (3.18g, 7.2 mmol) in anhydrous CH_2Cl_2 (40 mL), was added dimethyl diazomalonate (11.38 g, 72 mmol). At the top of the flask was installed a cold finger kept at -78°C. The green reaction mixture was warmed to rt at which time bubbling due to N_2 evolution was evident. An exotherm caused mild reflux for 15 minutes. The reaction was stirred for another 4 h. The mixture was concentrated in vacuo and purified by flash chromatography (eluting with 10:1 hexane/Et_2O to 5:1 hexane/Et_2O) to give 10.5 g (79%) of the dimethyl ester as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 6 H), 1.92 (s, 2 H), 1.04 (d, 4 H, J=3 Hz).

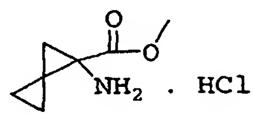
Step 2: Spiro[2.2]pentane-1,1-dicarboxylic acid methyl ester, shown below, was prepared as follows.



To the mixture of spiro[2.2]pentane-1,1-dicarboxylic acid dimethyl ester 800 mg (4.3 mmol) in 8 mL of MeOH and 2 mL of water was added KOH (240 mg, 4.3 mmol). This solution was stirred at rt for 2 days. It was then acidified with dilute HCl to pH 3

and extracted two times with ether. The combined organic phases were dried ($MgSO_4$) and concentrated to yield 600 mg (82%) of spiro[2.2]pentane-1,1-dicarboxylic acid methyl ester as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 6 H), 2.35 (d, 1 H, J=3 Hz), 2.26 (d, 1 H, J=3 Hz), 1.20 (m, 1 H), 1.15 (m, 1 H), 1.11 (m, 1 H), 1.05 (m, 1 H). LRMS: MS m/z 169 (M^+-1).

Step 3: 1-Amino-spiro[2.2]pentane-1-carboxylic acid methyl ester hydrochloride salt, shown below, was prepared as follows.

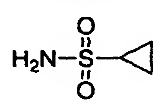


To a mixture of spiro[2.2]pentane-1,1-dicarboxylic acid methyl ester (400 mg, 2.30 mmol) in 3 mL of anhydrous t-BuOH was added 700 mg (2.50 mmol) of DPPA and 278 mg (2.70 mmol) of Et_3N. The mixture was heated at reflux for 21 h and then partitioned between H_2O and ether. The ether phase was dried over magnesium sulfate, filtered and concentrated in vacuo to yield an oil. To this oil was added 3 mL of a 4 M HCl/dioxane solution. This acidic solution was stirred at rt for 2 h and then concentrated in vacuo. The residue was triturated with ether to give 82 mg (20 %) of 1-amino-spiro[2.2]pentane-1-carboxylic acid methyl ester hydrochloride salt as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (br s, 3 H), 3.81 (s, 3 H), 2.16, (d, J=5.5 Hz, 1 H), 2.01 (d, J=5.5 Hz, 1 H), 1.49 (m, 1 H), 1.24, (m, 1 H), 1.12 (m, 2 H). LRMS of free amine: MS m/z 142 (M^++1).

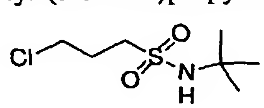
Section 2 of Example 12

The following P1\` intermediates were prepared as described:

1. Preparation of cyclopropylsulfonamide (Alternate route):



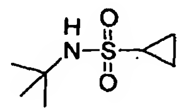
Step 1: Preparation of N-tert-Butyl-(3-chloro)propylsulfonamide



tert-Butylamine (3.0 mol, 315.3 mL) was dissolved in THF (2.5 L). The solution was cooled to – 20^{0}C. 3-Chloropropanesulfonyl chloride (1.5 mol, 182.4 mL) was added slowly. The reaction mixture was allowed to warm to rt and stirred for 24 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2.0 L). The resulting solution was washed with 1 N HCl (1.0 L), water (1.0 L), brine (1.0 L) and dried over Na_2SO_4. It was filtered and concentrated in vacuo to give a slightly yellow solid, which was crystallized from hexane to afford the product as a white solid (316.0 g, 99%).

^{1}H NMR ($CDCl_3$) 1.38 (s, 9H), 2.30-2.27 (m, 2H), 3.22 (t, J = 7.35 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 4.35 (b, 1H).

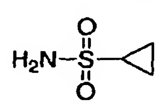
Step 2: preparation of Cyclopropanesulfonic acid tert-butylamide



To a solution of N-tert-butyl-(3-chloro)propylsulfonamide (2.14 g, 10.0 mmol) in THF (100 mL) was added n-BuLi (2.5 M in hexane, 8.0 mL, 20.0 mmol) at –78^{0}C. The reation mixture was allowed to warm up to room temperature over period of 1 h. The volatiles were removed in vacuo. The residue was partitioned between EtOAC and water (200 mL, 200 mL). The separated organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was recrystallized from hexane to yield the desired product as a white solid (1.0 g, 56%).

^{1}H NMR ($CDCl_3$) □ 0.98-1.00 (m, 2H), 1.18-1.19 (m, 2H), 1.39 (s, 9H), 2.48-2.51 (m, 1H), 4.19 (b, 1H).

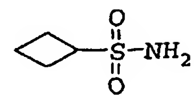
Step 3: preparation of cyclopropylsulfonamide



A solution of cyclopropanesulfonic acid tert-butylamide (110.0 g, 0.62 mol) in TFA (500 mL) was stirred at room temperature for 16 h. The volatile was removed in vacuo. The residue was recrystallized from EtOAC/hexane (60 mL/240 mL) to yield the desired product as a white solid (68.5 g, 91%).

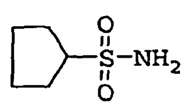
^{1}H NMR (DMSO-d_6) 0.84-0.88 (m, 2H), 0.95-0.98 (m, 2H), 2.41-2.58 (m, 1H), 6.56 (b, 2H).

2. Preparation of cyclobutyl sulfonamide



To a solution of 5.0 g (37.0 mmol) of cyclobutyl bromide in 30 mL of anhydrous diethyl ether (Et_2O) cooled to –78 °C was added 44 mL (74.8 mmol) of 1.7M *tert*-butyl lithium in pentanes and the solution slowly warmed to –35 °C over 1.5 h. This mixture was cannulated slowly into a solution of 5.0 g (37.0 mmol) freshly distilled sulfuryl chloride in 100 mL of hexanes cooled to –40 °C, warmed to 0 °C over 1 h and carefully concentrated in vacuo. This mixture was redissolved in Et_2O, washed once with some ice-cold water, dried ($MgSO_4$) and concentrated carefully. This mixture was redissolved in 20 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnite. The mixture was concentrated in vacuo to a crude yellow solid and was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 1.90 g (38%) of cyclobutylsulfonamide as a white solid. ^1H NMR ($CDCl_3$) δ 1.95-2.06 (m, 2H), 2.30-2.54 (m, 4H), 3.86 (p, J=8 Hz, 1H), 4.75 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 16.43, 23.93, 56.29. HRMS m/z $(M\text{-}H)^-$ calcd for $C_4H_8NSO_2$: 134.0276, found 134.0282.

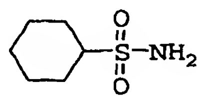
3. Preparation of cyclopentylsulfonamide



A solution of 18.5 mL (37.0 mmol) of 2M cyclopentyl-magnesium chloride in ether was added dropwise to a solution of 3.0 mL (37.0 mmol) freshly distilled sulfuryl chloride (obtained from Aldrich) in 100 mL of hexanes cooled to –78 °C. The mixture was warmed to 0 °C over 1 h and was then carefully concentrated in vacuo. This mixture was redissolved in Et_2O (200 mL), washed once with some ice-cold water (200 mL), dried ($MgSO_4$) and concentrated carefully. This mixture was redissolved in 35 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnite. The mixture was concentrated in vacuo to a crude yellow solid, the residue filtered through 50g of silica gel using 70% EtOAc-hexanes

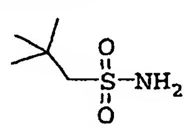
as the eluent and the solution was then concentrated. The residue was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 2.49 g (41%) of cyclopentylsulfonamide as a white solid. ^1H NMR ($CDCl_3$) δ 1.58-1.72 (m, 2H), 1.74-1.88 (m, 2H), 1.94-2.14 (m, 4H), 3.48-3.59 (m, 1H), 4.80 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 25.90, 28.33, 63.54; MS m/e 148 $(M-H)^-$.

4. Preparation of cyclohexyl sulfonamide



A solution of 18.5 mL (37.0 mmol) of 2M cyclohexylmagnesium chloride (TCI Americas) in ether was added dropwise to a solution of 3.0 mL (37.0 mmol) freshly distilled sulfuryl chloride in 100 mL of hexanes cooled to –78 °C. The mixture was warmed to 0 °C over 1 h and was then carefully concentrated in vacuo. This mixture was redissolved in Et_2O (200 mL), washed once with some ice-cold water (200 mL), dried ($MgSO_4$) and concentrated carefullyThis mixture was redissolved in 35 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnite. The mixture was concentrated in vacuo to a crude yellow solid, the residue filtered through 50g of silica gel using 70% EtOAc-hexanes as the eluent and was concentrated. The residue was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 1.66 g (30%) of cyclohexyl-sulfonamide as a white solid: ^1H NMR ($CDCl_3$) δ 1.11-1.37 (m, 3H), 1.43-1.56 (m, 2H), 1.67-1.76 (m, 1H), 1.86-1.96 (m, 2H), 2.18-2.28 (m, 2H), 2.91 (tt, *J*=12, 3.5 Hz, 1H), 4.70 (bs, 2H); ^{13C}H NMR ($CDCl_3$) δ 25.04, 25.04, 26.56, 62.74; MS m/e 162 $(M-1)^-$.

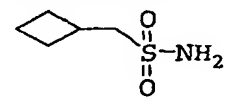
5. Preparation of Neopentylsulfonamide



Following the procedure for the prep of cyclohexyl sulfonamide, 49 mL (37 mmol) of 0.75M neopentylmagnesium chloride (Alfa) in ether was converted to 1.52g (27%)

of neopentylsulfonamide as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 3.12 (s, 2H), 4.74 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 29.46, 31.51, 67.38; MS m/e 150 $(M-1)^-$.

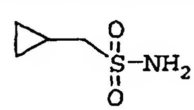
6. Preparation of cyclobutylcarbinyl-sulfonamide



A solution of 12.3 g (83 mmol) of cyclobutylcarbinyl bromide (Aldrich) and 13.7g (91 mmol) of sodium iodide in 150 mL of acetone was refluxed overnite and then cooled to rt. The inorganic solids were filtered off and the acetone and cyclopropylcarbinyl iodide (8.41g, 46%) distilled off at ambient and 150 torr at 80 °C, respectively.

A solution of 4.0 g (21.98 mmol) of cyclobutyl carbinyl iodide in 30 mL of anhydrous diethyl ether (Et_2O) cooled to −78 °C was cannulated into a solution of 17 mL (21.98 mmol) of 1.3M sec-butyl lithium in cyclohexanes and the solution was stirred for 5 min. To this mixture was cannulated a solution of 3.0 g (21.98 mmol) of freshly distilled sulfuryl chloride in 110 mL of hexanes cooled to −78 °C, the mixture warmed to rt over 1 h and was then carefully concentrated in vacuo. This mixture was redissolved in Et_2O, washed once with some ice-cold water, dried ($MgSO_4$) and concentrated carefully. This mixture was redissolved in 30 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnite. The mixture was concentrated in vacuo to a crude yellow solid and was recrystallized from the minimum amount of CH_2Cl_2 in hexanes with 1-2 drops of MeOH to afford 1.39 g (42%) of cyclobutyl carbinylsulfonamide as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.81-2.03 (m, 4H), 2.14-2.28 (m, 2H), 2.81-2.92 (m, 1H), 3.22 (d, J=7 Hz, 2H), 4.74 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 19.10, 28.21, 30.64, 60.93; MS m/e 148 $(M-1)^-$. time: 1.73, method B), 818 (M^++H)

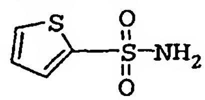
7. Preparation of cyclopropylcarbinyl-sulfonamide



Using the procedure employed for the preparation of cyclobutylcarbinyl-sulfonamide, cyclopropylcarbinyl sulfonamide was prepared from cyclopropylcarbinyl bromide

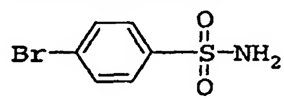
(Aldrich) (see also *JACS* 1981, p.442-445). ^{1}H NMR ($CDCl_3$) δ 0.39-0.44 (m, 2H), 0.67-0.76 (m, 2H), 1.13-1.27 (m, 1H), 3.03 (d, J=7.3 Hz, 2H), 4.74 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 4.33, 5.61, 59.93; MS m/e 134 (M-1).

8. Preparation of 2-thiophene sulfonamide



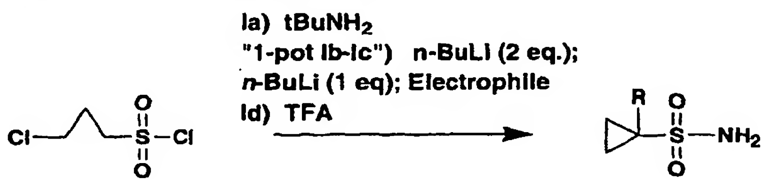
Prepared from 2-thiophene sulfonylchloride which was purchased from Aldrich using the method of Steinkopf and Hoepner, *Justus Liebigs Ann. Chem.*, *501*, **1933**, p.174-182.

9. Preparation of 4-Bromobenzenesulfonamide



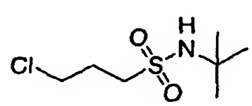
4-bromophenylsulfonamide was prepared by treatment of commercially available 4-bromosulfonyl chloride with saturated ammonia in THF

10. Preparation of 1-Substituted Cyclopropanesulfonamides

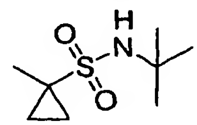


Step 1 Preparation of *N-tert*-Butyl-(3-chloro)propylsulfonamide

(Described above)

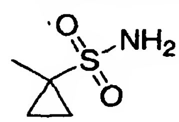


Steps 2 Preparation of *N-tert*-Butyl-(1-methyl)cyclopropyl-sulfonamide.



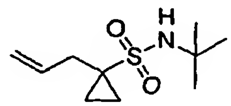
A solution of *N-tert*-Butyl-(3-chloro)propylsulfonamide (4.3 g, 20 mmol) was dissolved in dry THF (100 mL) and cooled to – 78 °C. To this solution was added *n*-BuLi (17.6 mL, 44 mmol, 2.5 M in hexane) slowly. The dry ice bath was removed and the reaction mixture was allowed to warm to rt over a period of 1.5 h. This mixture was then cooled to - 78°C, and a solution of *n*-BuLi (20 mmol, 8 mL, 2.5 M in hexane) was added. The reaction mixture was warmed to rt, recooled to –78 °C over a period of 2 h and a neat solution of methyliodide (5.68 g, 40 mmol) added. The reaction mixture was allowed to warm to rt overnight, quenched with saturated NH_4Cl (100 mL) at rt. It was extracted with EtOAc (100 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil which was crystallized from hexane to afford the product as a slightly yellow solid (3.1 g, 81%): ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 2H), 1.36 (s, 9H), 1.52 (m, 2H), 1.62 (s, 3H), 4.10 (bs, 1H)

Step 3 Preparation of Example 3, 1-methylcyclopro-pylsulfonamide.



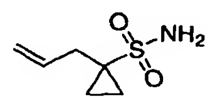
A solution of *N-tert*-Butyl-(1-methyl)cyclopropylsulfonamide (1.91 g, 10 mmol) was dissolved in TFA (30 mL), and the reaction mixture stirred at rt for 16 h. The solvent was removed in vacuo to give a yellow oil which was crystallized from EtOAc / hexane (1 : 4, 40 mL) to yield Example 3, 1-methylcyclopropylsulfonamide, as a white solid (1.25 g, 96%): ^{1}H NMR ($CDCl_3$) δ 0.84 (m, 2H), 1.41 (m, 2H), 1.58 (s, 3H), 4.65 (bs, 2H). Anal. Calcd. For $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36. Found: C, 35.67; H, 6.80; N, 10.40.

Preparation of *N-tert*-Butyl-(1-allyl)cyclopropylsulfonamide.



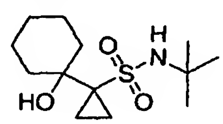
Step 1 This compound, *N-tert*-Butyl-(1-allyl)cyclopropylsulfonamide, was obtained in 97% yield according to the procedure described in the synthesis *of N-tert*-Butyl-(1-methyl)cyclopropylsul-fonamide except 1.25 equivalents of allyl bromide were used as electrophile. The compound was taken directly into the next reaction without purification: ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 2H), 1.34 (s, 9H), 1.37 (m, 2H), 2.64 (d, J = 7.3 Hz, 2H), 4.25 (bs, 1H), 5.07-5.10 (m, 2H), 6.70-6.85 (m, 1H).

Step 2 Preparation of Example 4, 1-allylcyclopro-pylsulfonamide.



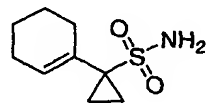
This compound, 1-allylcyclopropylsulfonamide, was obtained in 40% yield from *N-tert*-butyl-(1-allyl)cyclopropylsulfonamide according to the procedure described in the synthesis of 1-Methylcyclopropylsulfonamide. The compound was purified by column chromotography over SiO_2 using 2% MeOH in CH_2Cl_2 as the eluent: ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 2 H), 1.37 (m, 2 H), 2.66 (d, J=7.0 Hz, 2 H), 4.80 (s, 2 H), 5.16 (m, 2 H), 5.82 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.2, 35.6, 40.7, 119.0, 133.6.

Preparation of *N-tert*-Butyl-[1-(1-hydroxy)cyclohexyl]-cyclopropylsulfonamide.



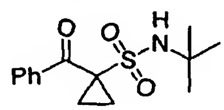
Step 1 This compound was obtained in 84% yield using to the procedure described for the synthesis of *N-tert*-Butyl-(1-methyl)cyclopropylsul-fonamide except 1.30 equivalents of cyclohexanone were used, followed by recrystallization from the minimum amount of 20% EtOAc in hexane: ^{1}H NMR ($CDCl_3$) δ 1.05 (m, 4H), 1.26 (m, 2H), 1.37 (s, 9H), 1.57-1.59 (m, 6H), 1.97 (m, 2H), 2.87 (bs, 1H), 4.55 (bs, 1H).

Steps 2 Preparation of 1-(1-cyclohexenyl)cyclopropyl-sulfonamide.



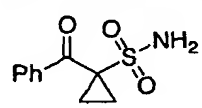
This compound, 1-(1-cyclohexenyl)-cyclopropylsulfonamide, was obtained in 85% yield from *N*-tert-butyl-[1-(1-hydroxy)cyclohexyl]-cyclopropylsulfonamide using the procedure described for the synthesis of 1-methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of EtOAc and hexane: ^{1}H NMR (DMSO-d_6) δ 0.82 (m, 2 H), 1.28 (m, 2 H), 1.51 (m, 2 H), 1.55 (m, 2 H), 2.01 (s, 2 H), 2.16 (s, 2 H), 5.89 (s, 1 H), 6.46 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 11.6, 21.5, 22.3, 25.0, 27.2, 46.9, 131.6, 132.2; LR-MS (ESI): 200 (M^+-1).

Preparation of *N-tert*-Butyl-(1-benzoyl)cyclopropyl-sulfonamide.



Step 1 This compound was obtained in 66% yield using the procedure described for the synthesis of *N-tert*-Butyl-(1-methyl)cyclopropylsulfonamide except 1.2 equivalents of methyl benzoate was used as the electrophile. The compound was purified by column chromatography over SiO_2 using 30% to 100% CH_2Cl_2 in hexane: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.52 (m, 2H), 1.81 (m, 2H), 4.16 (bs, 1H), 7.46 (m, 2H), 7.57 (m, 1H), 8.05 (d, J = 8.5 Hz, 2H).

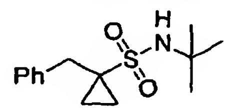
Step 2 Preparation 1-benzoylcyclo-propylsulfonamide.



Step 2 This compound, 1-benzoylcyclopropyl-sulfonamide, was obtained in 87% yield from *N-tert*-butyl(1-benzoyl)cyclopropylsul-fonamide using the procedure described for the synthesis of 1-Methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of EtOAc in hexane: ^{1}H NMR (DMSO-d_6) δ 1.39 (m, 2 H), 1.61 (m, 2 H), 7.22 (s, 2 H), 7.53 (t, J=7.6 Hz, 2 H), 7.65 (t,

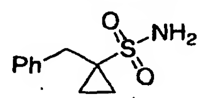
J=7.6 Hz, 1 H), 8.06 (d, J=8.2 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 12.3, 48.4, 128.1, 130.0, 133.4, 135.3, 192.0.

Preparation of *N-tert*-Butyl-(1-benzyl)cyclopropyl-sulfonamide.



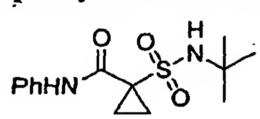
Step 1 This compound was obtained in 60% yield using the procedure described for the synthesis of *N-tert*-Butyl-(1-methyl)cyclopropylsulfonamide except 1.05 equivalents of benzyl bromide were used, followed by trituration with 10% EtOAc in hexane: ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 2H), 1.36 (m, 2H), 1.43 (s, 9H), 3.25 (s, 2H), 4.62 (bs, 1H), 7.29-7.36 (m, 5H).

Steps 2 Preparation of 1-Benzylcyclo-propylsulfonamide.



This compound, Example 7, 1-Benzylcyclopropylsulfonamide, was obtained in 66% yield from *N-tert*-butyl(1-benzyl)cyclopropylsul-fonamide using the procedure described for the synthesis of 1-Methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of 10% EtOAc in hexane: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 2H), 1.42 (m, 2 H), 3.25 (s, 2 H), 4.05 (s, 2 H), 7.29 (m, 3 H), 7.34 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.1, 36.8, 41.9, 127.4, 128.8, 129.9, 136.5.

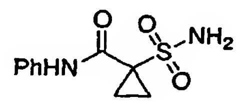
Preparation of *N-tert*-Butyl-(1-phenylaminocarboxy)-cyclopropylsulfonamide.



Step1 This compound was obtained in 42% yield using the procedure described for the synthesis of *N-tert*-Butyl-(1-methyl)cyclopropylsulfonamide using 1 equivalent of phenylisocyanate, followed by recrystallization from the minimum

amount of EtOAc in hexane ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.67-1.71 (m, 4H), 4.30 (bs, 1H); 7.10 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 2H).

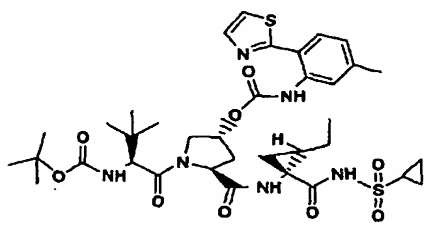
Steps 2 Preparation of Example 8, 1-(Phenylamino-carboxy)cyclopropyl-sulfonamide.

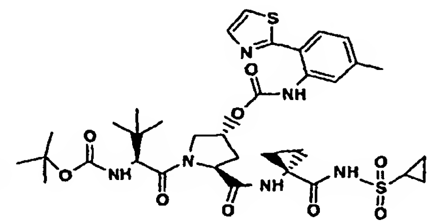


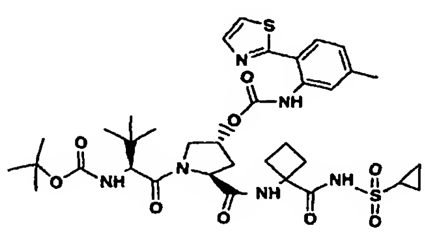
Step 2 1-(Phenylaminocarboxy)cyclopropylsulfonamide, was obtained in 75% yield from *N-tert*-butyl(1-phenylaminocarboxy)cyclopropylsulfonamide using the procedure described for the synthesis of 1-Methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of EtOAc in hexane: ^1H NMR ($CDCl_3$) δ 1.70 (m, 2 H), 1.75 (m, 2 H), 4.85 (s, 2 H), 7.16 (t, *J*=7.6 Hz, 1 H), 7.35 (t, *J*=7.6 Hz, 2 H), 7.53 (d, *J*=8.2 Hz, 2 H), 9.25 (s, 1 H).

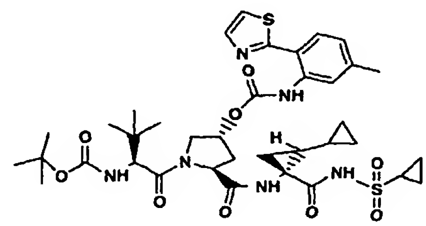
Section three of Example 12

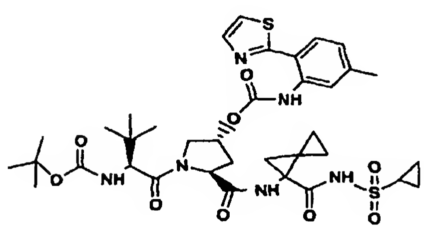
The following compounds can be made using the intermediates described herein and by analogy to processes and experimentation described herein.

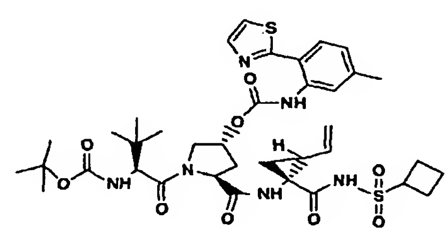


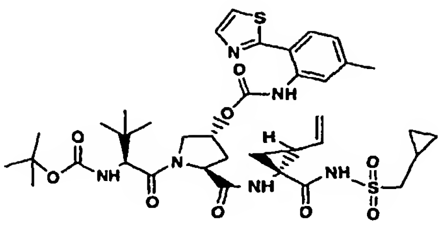


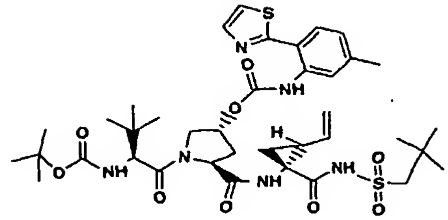


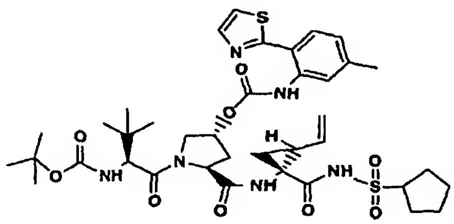


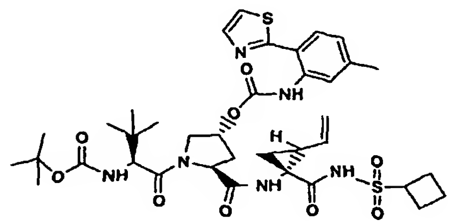


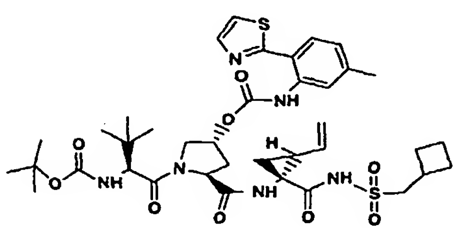


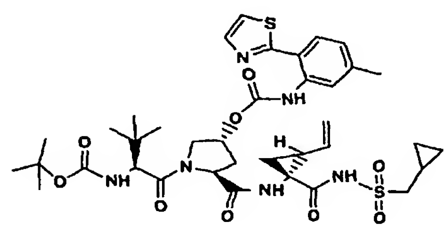


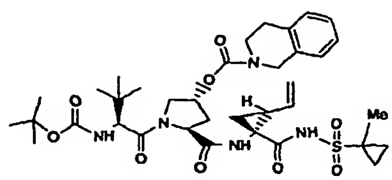


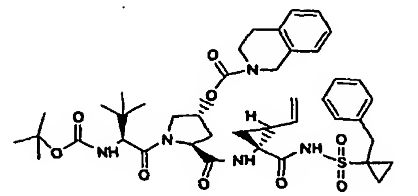


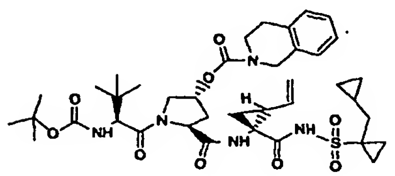


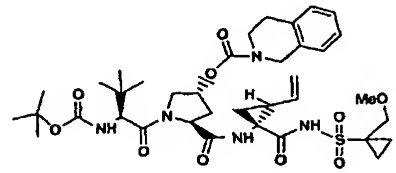


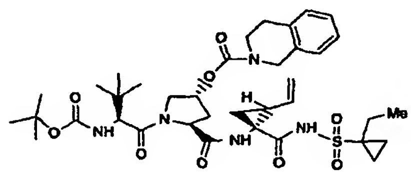


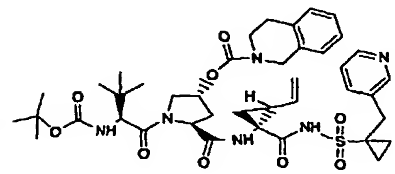


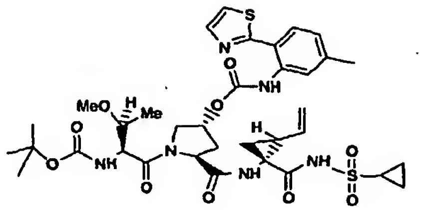


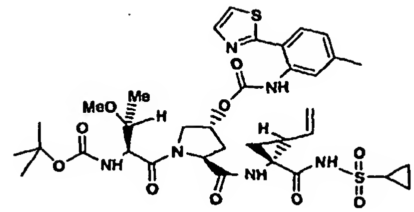


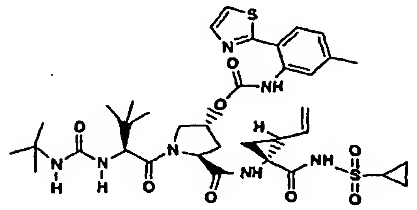


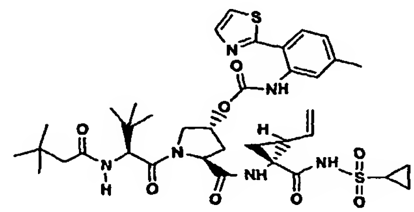


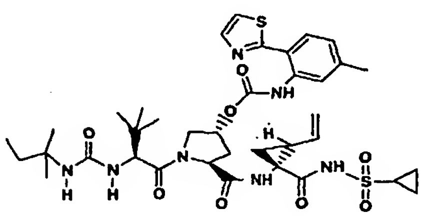


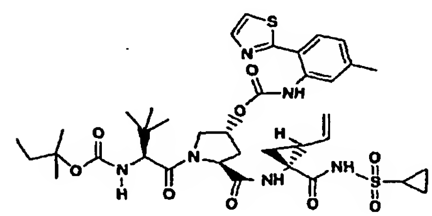

S
N
O
NH
MeO
H
Me
O
NH
O
N
O
H
NH
O
NH
O
S
O

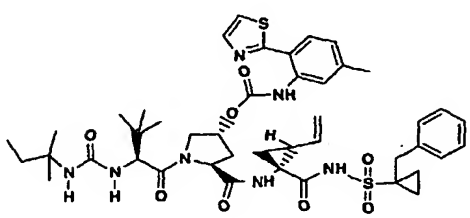

S
N
O
NH
MeO
Me
H
O
NH
O
N
O
H
NH
O
NH
O
S
O

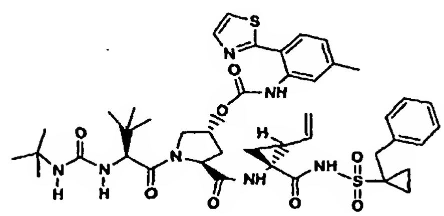

S
N
O
NH
O
N
H
N
H
O
N
O
NH
O
NH
O
S
O

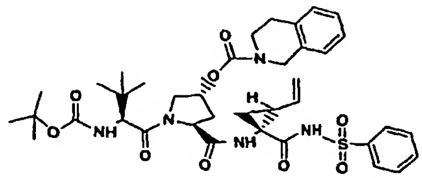

S
N
O
NH
O
O
N
H
O
N
H
O
NH
O
NH
O
S
O

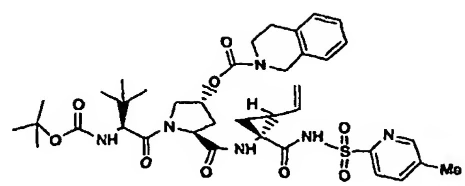

S
N
O
NH
O
N
H
N
H
O
N
H
O
NH
O
NH
O
S
O

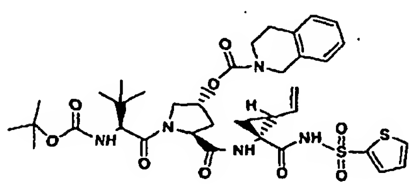

S
N
O
NH
O
O
N
H
O
N
H
O
NH
O
NH
O
S
O

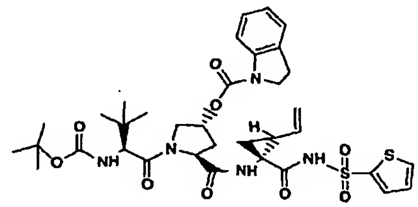

S
N
O
NH
O
N
H
N
H
O
N
H
O
NH
O
NH
O
S
O

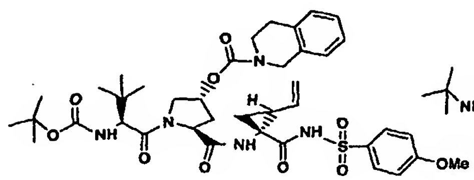

S
N
O
NH
O
N
H
N
H
O
N
H
O
NH
O
NH
O
S
O

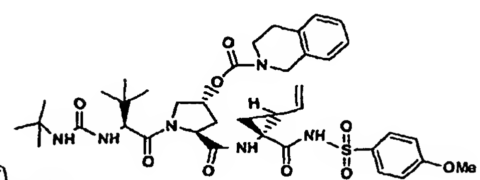


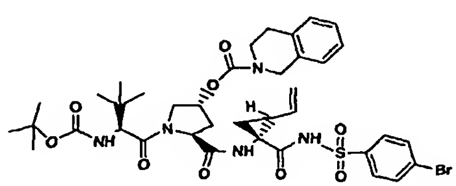












Example 13

Biological Studies

Recombinant HCV NS3/4A protease complex FRET peptide assay

The purpose of this in vitro assay was to measure the inhibition of HCV NS3 protease complexes, derived from the BMS, H77C or J416S strains, as described below, by compounds of the present invention. This assay provides an indication of how effective compounds of the present invention would be in inhibiting HCV proteolytic activity.

Serum from an HCV-infected patient was obtained from Dr. T. Wright, San Francisco Hospital. An engineered full-length cDNA (compliment deoxyribonucleic acid) template of the HCV genome (BMS strain) was constructed from DNA fragments obtained by reverse transcription-PCR (RT-PCR) of serum RNA (ribonucleic acid) and using primers selected on the basis of homology between other genotype 1a strains. From the determination of the entire genome sequence, a genotype 1a was assigned to the HCV isolate according to the classification of Simmonds et al. (See P Simmonds, KA Rose, S Graham, SW Chan, F McOmish, BC Dow, EA Follett, PL Yap and H Marsden, J. Clin. Microbiol., 31(6), 1493-1503 (1993)). The amino acid sequence of the nonstructural region, NS2-5B, was shown to be >97% identical to HCV genotype 1a (H77C) and 87% identical to genotype 1b (J4L6S). The infectious clones, H77C (1a genotype) and J4L6S (1b genotype) were obtained from R. Purcell (NIH) and the sequences are published in Genbank (AAB67036, see Yanagi,M., Purcell,R.H., Emerson,S.U. and Bukh,J. Proc. Natl. Acad. Sci. U.S.A. 94(16),8738-8743 (1997); AF054247, see Yanagi,M., St Claire,M., Shapiro,M., Emerson,S.U., Purcell,R.H. and Bukh,J, Virology 244 (1), 161-172. (1998)).

The BMS, H77C and J4L6S strains were used for production of recombinant NS3/4A protease complexes. DNA encoding the recombinant HCV NS3/4A protease complex (amino acids 1027 to 1711) for these strains were manipulated as described by P. Gallinari et al. (see Gallinari P, Paolini C, Brennan D, Nardi C,

Steinkuhler C, De Francesco R. Biochemistry. 38(17):5620-32, (1999)). Briefly, a three-lysine solubilizing tail was added at the 3'-end of the NS4A coding region. The cysteine in the P1 position of the NS4A-NS4B cleavage site (amino acid 1711) was changed to a glycine to avoid the proteolytic cleavage of the lysine tag. Furthermore, a cysteine to serine mutation was introduced by PCR at amino acid position 1454 to prevent the autolytic cleavage in the NS3 helicase domain. The variant DNA fragment was cloned in the pET21b bacterial expression vector (Novagen)and the NS3/4A complex was expressed in Escherichia. coli strain BL21 (DE3) (Invitrogen) following the protocol described by P. Gallinari et al. (see Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, De Francesco R., J Virol. 72(8):6758-69 (1998)) with modifications. Briefly, NS3/4A expression was induced with 0.5mM Isopropyl β-D-1-thiogalactopyranoside (IPTG) for 22hr at 20°C. A typical fermentation (10L) yielded approximately 80g of wet cell paste. The cells were resuspended in lysis buffer (10mL/g) consisting of 25mM N-(2-Hydroxyethyl)Piperazine-N'-(2-Ethane Sulfonic acid) (HEPES), pH7.5, 20% glycerol, 500mM Sodium Chloride (NaCl), 0.5% Triton-X100, 1ug/ml lysozyme, 5mM Magnesium Chloride ($MgCl_2$), 1ug/ml DnaseI, 5mM β-Mercaptoethanol (βME), Protease inhibitor - Ethylenediamine Tetraacetic acid (EDTA) free (Roche), homogenized and incubated for 20 mins at 4°C. The homogenate was sonicated and clarified by ultra-centrifugation at 235000g for 1hr at 4°C. Imidazole was added to the supernatant to a final concentration of 15mM and the pH adjusted to 8.0. The crude protein extract was loaded on a Nickel - Nitrilotriacetic acid (Ni-NTA) column pre-equilibrated with buffer B (25mM HEPES, pH8.0, 20% glycerol, 500mM NaCl, 0.5% Triton-X100, 15mM imidazole, 5mM βME). The sample was loaded at a flow rate of 1mL/min. The column was washed with 15 column volumes of buffer C (same as buffer B except with 0.2% Triton-X100). The protein was eluted with 5 column volumes of buffer D (same as buffer C except with 200mM Imidazole).

NS3/4A protease complex-containing fractions were pooled and loaded on a desalting column Superdex-S200 pre-equilibrated with buffer D (25mM HEPES, pH7.5, 20% glycerol, 300mM NaCl, 0.2% Triton-X100, 10mM βME). Sample was loaded at a flow rate of 1mL/min. NS3/4A protease complex-containing fractions

were pooled and concentrated to approximately 0.5mg/ml. The purity of the NS3/4A protease complexes, derived from the BMS, H77C and J4L6S strains, were judged to be greater than 90% by SDS-PAGE and mass spectrometry analyses.

The enzyme was stored at -80°C, thawed on ice and diluted prior to use in assay buffer. The substrate used for the NS3/4A protease assay was RET S1 (Resonance Energy Transfer Depsipeptide Substrate; AnaSpec, Inc. cat # 22991)(FRET peptide), described by Taliani et al. in Anal. Biochem. 240(2):60-67 (1996). The sequence of this peptide is loosely based on the NS4A/NS4B natural cleavage site except there is an ester linkage rather than an amide bond at the cleavage site. The peptide substrate was incubated with one of the three recombinant NS3/4A complexes, in the absence or presence of a compound of the present invention, and the formation of fluorescent reaction product was followed in real time using a Cytofluor Series 4000.

The reagents were as follow: HEPES and Glycerol (Ultrapure) were obtained from GIBCO-BRL. Dimethyl Sulfoxide (DMSO) was obtained from Sigma. β-Mercaptoethanol was obtained from Bio Rad.
Assay buffer: 50mM HEPES, pH7.5; 0.15M NaCl; 0.1% Triton; 15% Glycerol;10mM βME. Substrate: 2 μM final concentration (from a 2mM stock solution in DMSO stored at -20°C). HCV NS3/4A type 1a (1b), 2-3 nM final concentration (from a 5μM stock solution in 25mM HEPES, pH7.5, 20% glycerol, 300mM NaCl, 0.2% Triton-X100, 10mM βME). For compounds with potencies approaching the assay limit, the assay was made more sensitive by adding 50 μg/ml BSA to the assay buffer and reducing the end protease concentration to 300 pM.

The assay was performed in a 96-well polystyrene black plate from Falcon. Each well contained 25μl NS3/4A protease complex in assay buffer, 50μl of a compound of the present invention in 10% DMSO/assay buffer and 25μl substrate in assay buffer. A control (no compound) was also prepared on the same assay plate. The enzyme complex was mixed with compound or control solution for 1 min before

initiating the enzymatic reaction by the addition of substrate. The assay plate was read immediately using the Cytofluor Series 4000 (Perspective Biosystems). The instrument was set to read an emission of 340nm and excitation of 490nm at 25°C. Reactions were generally followed for approximately 15 minutes.

The percent inhibition was calculated with the following equation:

$$100 - [(\delta F_{inh}/\delta F_{con}) \times 100]$$

where δF is the change in fluorescence over the linear range of the curve. A non-linear curve fit was applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) was calculated by the use of Excel Xl-fit software using the equation, y=A+((B-A)/(1+((C/x)^D))).

All of the compounds tested were found to have IC50s of 2.3 μM or less. Further, compounds of the present invention, which were tested against more than one type of NS3/4A complex, were found to have similar inhibitory properties though the compounds uniformly demonstrated greater potency against the 1b strains as compared to the 1a strains.

Specificity Assays

The specificity assays were performed to demonstrate the selectivity of the compounds of the present invention in inhibiting HCV NS3/4A protease as compared to other serine or cysteine proteases.

The specificities of compounds of the present invention were determined against a variety of serine proteases: human sputum elastase (HS), porcine pancreatic elastase (PPE) and human pancreatic chymotrypsin and one cysteine protease: human liver cathepsin B. In all cases a 96-well plate format protocol using colorimetric p-nitroaniline (pNA) substrate specific for each enzyme was used as described previously (Patent WO 00/09543) with some modifications to the serine protease

assays. All enzymes were purchased from Sigma while the substrates were from Bachem.

Each assay included a 2hr enzyme-inhibitor pre-incubation at RT followed by addition of substrate and hydrolysis to ~30% conversion as measured on a Spectramax Pro microplate reader. Compound concentrations varied from 100 to 0.4 μM depending on their potency.

The final conditions for each assay were as follows:

50mM Tris(hydroxymethyl)aminomethane hydrochloride (Tris-HCl) pH8, 0.5M Sodium Sulfate (Na_2SO_4), 50mM NaCl, 0.1mM EDTA, 3% DMSO, 0.01% Tween-20 with:
133 μM succ-AAA-pNA and 20nM HS or 8nM PPE; 100 μM succ-AAPF-pNA and 250pM Chymotrypsin.

100mM $NaHPO_4$ (Sodium Hydrogen Phosphate) pH 6, 0.1mM EDTA, 3% DMSO, 1mM TCEP (Tris(2-carboxyethyl)phosphine hydrochloride), 0.01% Tween-20, 30μM Z-FR-pNA and 5nM Cathepsin B (enzyme stock activated in buffer containing 20mM TCEP before use).

The percentage of inhibition was calculated using the formula:

$$[1-((UV_{inh}-UV_{blank})/(UV_{ctl}-UV_{blank}))] \times 100$$

A non-linear curve fit was applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) was calculated by the use of Excel Xl-fit software.

HCV Replicon Cell-based Assay

An HCV replicon whole cell system was established as described by Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R., Science 285(5424):110-3 (1999). This system enabled us to evaluate the effects of our HCV Protease compounds on HCV RNA replication. Briefly, using the HCV strain 1B sequence described in the Lohmann paper (Assession number:AJ238799), an HCV cDNA was generated encoding the 5' internal ribosome entry site (IRES), the neomycin resistance gene, the EMCV (encephalomyocarditis viurs)-IRES and the HCV nonstructural proteins, NS3-NS5B, and 3' non-translated region (NTR). In vitro transcripts of the cDNA were transfected into the human hepatoma cell line, Huh7. Selection for cells constitutively expressing the HCV replicon was achieved in the presence of the selectable marker, neomycin (G418). Resulting cell lines were characterized for positive and negative strand RNA production and protein production over time.

Huh7 cells, constitutively expressing the HCV replicon, were grown in Dulbecco's Modified Eagle Media (DMEM) containing 10% Fetal calf serum (FCS) and 1mg/ml G418 (Gibco-BRL). Cells were seeded the night before (1.5×10^4 cells/well) in 96-well tissue-culture sterile plates. Compound and no compound controls were prepared in DMEM containing 4% FCS, 1:100 Penicillin / Streptomysin, 1:100 L-glutamine and 5% DMSO in the dilution plate (0.5% DMSO final concentration in the assay). Compound / DMSO mixes were added to the cells and incubated for 4 days at 37°C. After 4 days, plates were rinsed thoroughly with Phosphate-Buffered Saline (PBS) (3 times 150μl). The cells were lysed with 25μl of a lysis assay reagent containing the FRET peptide (RET S1, as described for the in vitro enzyme assay). The lysis assay reagent was made from 5X cell Luciferase cell culture lysis reagent(Promega #E153A) diluted to 1X with distilled water, NaCl added to 150 mM final, the FRET peptide diluted to 10 μM final from a 2 mM stock in 100% DMSO. The plate was then placed into the Cytofluor 4000 instrument which had been set to 340nm excitation / 490 emission, automatic mode for 21 cycles

and the plate read in a kinetic mode. EC_{50} determinations were carried out as described for the IC_{50} determinations.

As a secondary assay, EC_{50} determinations from the replicon FRET assay were confirmed in a quantitative RNA assay. Cells were lyzed using the Rneasy kit (Qiagen). Purified total RNA was normalized using RiboGreen (Jones LJ, Yue ST, Cheung CY, Singer VL, Anal. Chem., 265(2):368-74 (1998)) and relative quantitation of HCV RNA expression assessed using the Taqman procedure (Kolykhalov AA, Mihalik K, Feinstone SM, Rice CM, Journal of Virology 74, 2046-2051 (2000)) and the Platinum Quantitative RT-PCR Thermoscript One-Step kit (Invitrogen cat # 11731-015). Briefly, RNA made to a volume of 5μl (≤ 1ng) was added to a 20μl Ready-Mix containing the following: 1.25X Thermoscript reaction mix (containing Magnesium Sulfate and 2-deoxynucleoside 5'-triphosphates (dNTPs)), 3mM dNTPs, 200nM forward primer (sequence: 5'-gggagagccatagtggtctgc-3'), 600nM reverse primer (5'-cccaaatctccaggcattga-3'), 100nM probe (5'-6-FAM-cggaattgccaggacgaccgg-BHQ-1-3')(FAM: Fluorescein-aminohexyl amidite; BHQ: Black Hole Quencher), 1μM Rox reference dye (Invitrogen cat # 12223-012) and Thermoscript Plus Platinum Taq polymerase mixture. All primers were designed with ABI Prism 7700 software and obtained from Biosearch Technologies, Novato, CA. Samples containing known concentrations of HCV RNA transcript were run as standards. Using the following cycling protocol (50°C, 30 min; 95°C, 5 min; 40 cycles of 95°C, 15 sec, 60°C, 1 min), HCV RNA expression was quantitated as described in the Perkin Elmer manual using the ABI Prism 7700 Sequence Detector.

The luciferase reporter assay was also used to confirm compound potency in the replicon. Utilization of a replicon luciferase reporter assay was first described by Krieger et al (Krieger N, Lohmann V, and Bartenschlager R, J. Virol. 75(10):4614-4624 (2001)). The replicon construct described for our FRET assay was modified by replacing the resistance gene neomycin with the Blasticidin-resistance gene fused to the N-terminus of the humanized form of Renilla luciferase (restriction sites Asc1 / Pme1 used for the subcloning). The adaptive mutation at position 1179 (serine to

isoleucine) was also introduced (Blight KJ, Kolykhalov, AA, Rice, CM, Science 290(5498):1972-1974). The luciferase reporter assay was set up by seeding huh7 cells the night before at a density of 2 x 10^6 cells per T75 flask. Cells were washed the next day with 7.5ml Opti-MEM. Following the Invitrogen protocol, 40 μl DMRIE-C was vortexed with 5 ml Opti-MEM before adding 5 μg HCV reporter replicon RNA. The mix was added to the washed huh7 cells and left for 4 hours at 37°C. In the mean time, serial compound dilutions and no compound controls were prepared in DMEM containing 10% FCS and 5% DMSO in the dilution plate (0.5% DMSO final concentration in the assay). Compound / DMSO mixes were added to each well of a 24-well plate. After 4 hours, the transfection mix was aspirated, and cells washed with 5ml of Opti-MEM before trypsinization. Trypsinized cells were resuspended in 10% DMEM and seeded at 2 x 10^4 cells/well in the 24-well plates containing compound or no compound controls. Plates were incubated for 4 days. After 4 days, media was removed and cells washed with PBS. 100μl 1x Renilla Luciferase Lysis Buffer (Promega) was immediately added to each well and the plates either frozen at -80°C for later analysis, or assayed after 15 mins of lysis. Lysate (40μl) from each well was transferred to a 96-well black plate (clear bottom) followed by 200 μl 1x Renilla Luciferase assay substrate. Plates were read immediately on a Packard TopCount NXT using a luminescence program.

The percentage inhibition was calculated using the formula below:

$$\%\ control = \frac{\text{average luciferase signal in experimental wells (+ compound)}}{\text{average luciferase signal in DMSO control wells (- compound)}}$$

T25 values were graphed and analyzed using XLFit to obtain the EC_{50} value.

Biological Examples

Representative compounds of the invention were assessed in the HCV replicon cell assay and/or in several of the outlined specificity assays. For example, Compound 8 was found to have an IC_{50} of 51 nM against the NS3/4A BMS strain in the enzyme assay. Similar potency values were obtained with the published H77C (IC_{50} of 11 nM) and J4L6S (IC_{50} of 9.5 nM) strains. The EC_{50} value in the replicon assay was 284 nM.

In the specificity assays, the same compound was found to have the following activity: HS > 100 μM; PPE > 100 μM; Chymotrypsin > 100 μM; Cathepsin B > 100 μM. These results indicate this family of compounds are highly specific for the NS3 protease and many of these members inhibit HCV replicon replication.

The compounds of the current invention were tested using the assays described above and found to have activities in the following ranges:

IC_{50} Activity Ranges: A is > 10 micromolar (μM); B is 1-10 μM; C is 0.1 - 1 μM, D is < 0.1 μM

EC_{50} Activity Ranges: is > 10 micromolar (μM); B is 1-10 μM; C is 0.1 - 1 μM, D is < 0.1 μM

The structures of compounds used in the tests can be found from the Patent compound number shown in the Activity Table below.

In accordance with the present invention, preferred compounds have a biological activity (EC_{50}) of 10 μM or less, more preferably 1 μM or less and most preferably 0.1 μM or less.

Activity Table		
Cmpd Number	IC50 range	EC50 range
1	C	B
2	C	B
3	D	B
4	C	A
5	C	B
6	D	B
7	C	B
8	D	C
9	D	C
10	C	A
11	C	B
12	B	A
13	C	A
14	C	B
15	D	B
16	C	B
17	C	B
18	C	A
19	D	D
20	D	B
21	D	C
22	B	
23	D	C
24	C	A
25	D	B
26	D	B
27	D	B
28	C	B
29	D	C
30	D	D
31	D	C
32	D	D
33	C	C
34	C	B
35	D	A
36	D	C
37	D	B
38	D	C
39	D	C
40	D	B
41	D	B
42	D	B

43	C	A
44	D	B
45	D	C
46	C	B
47	C	A
48	D	C
49	C	B
50	D	B
51	C	B
52	C	A
53	D	B
54	C	B
55	D	C
56	D	C
57	C	B
58	B	
59	C	B
60	D	C
61	B	
62	B	
63	C	B
64	D	C
65	D	C
66	D	B
67	D	C
68	B	
69	C	A
70	C	A
71	D	C
72	D	B
73	D	A
74	D	C
75	C	A
76	D	C
77a	C	B
77b	C	A
78	C	A
79	D	C
80	D	D
81	D	D
82	D	C
83	D	D
84	D	C
85	D	C
86	D	C
87	D	D

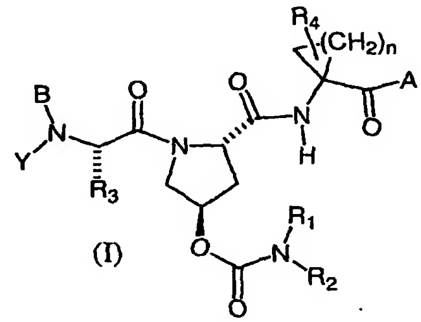
88	D	A
89	D	C
90	D	D
91	D	C
92	D	D
93	D	C
94	D	D
95	D	C
96	D	D
97	D	D
98	D	D
99	D	D
100	D	D
101	D	B
102	A	
103	A	
104	B	
105	A	
106	A	
107	A	
108	A	
109	A	
110	D	C
111	D	C

Although the invention has been described with respect to specific aspects, those skilled in the art will recognize that other aspects, not specifically described herein, are intended to be included within the scope of the claims that follow.

CLAIMS

What is claimed is:

1. A compound of Formula I:



(I)

and enantiomers , diastereomers and pharmaceutically acceptable salts thereof, wherein:

(a) R_1 is: H, C_{1-6} alkyl, C_{2-10} alkenyl or C_{6-10} aryl, all of which may be substituted with halo, cyano, nitro, C_{1-6} alkoxy, amido, amino or phenyl;

R_2 is:

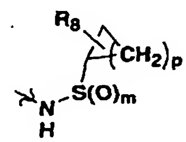
(i) C_{1-6} alkyl; C_{1-6} alkyl substituted with a carboxy (C_{1-6} alkyl); C_{3-7} cycloalkyl; C_{3-6} cycloalkyl (C_{6-10} aryl); C_{2-10} alkenyl; C_{1-3} alkyl (C_{6-10} aryl); all of which may be substituted from one to three times with halo, C_{1-3} alkyl or C_{1-3} alkoxy; or R^2 is C_{5-9} heterocycle, which may be substituted from one to three times with halo, C_{1-4} alkyl, (C_{1-6} alkyl) carboxy or phenyl; or

(ii) C_{6-10} aryl, which may be substituted from one to three times with the following: halo; C_{1-6} alkyl which itself may be substituted with one to three halo; C_{1-6} alkoxy; nitro; thio (C_{1-6} alkyl); phenyl; C_{1-6} alkanoyl; benzoyl; benzoyl oxime; carboxy; carboxy (C_{1-6} alkyl); (C_{1-6} alkyl) carboxy; phenoxy; (C_{1-6} alkyl) carboxy (C_{1-6} alkyl); or C_{6-10} aryl which may be substituted with a C_{5-9} heterocycle, which heterocycle includes one to three nitrogen, oxygen or sulfur atoms and

which heterocycle itself may be substituted with C_{1-3} alkyl, C_{1-3} alkoxy, $-CF_3$ or (C_{1-3} alkyl) carboxy; or

(b) R_1 and R_2 may join to form a 5 or 6 membered heterocycle, or join to form a 5 or 6 membered heterocycle fused with one or two C_6 aryl groups;

(d) A is -OH, C_{1-6} alkoxy, $-N(H)SO_mR^5$



where p is 1, 2 or 3, and R_8 is trialkylsilane; halo; C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-\overset{O}{\overset{\|}{C}}-R_9$ wherein R_9 is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-\overset{O}{\overset{\|}{C}}-OR_{10}$ wherein R_{10} isC_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-\overset{O}{\overset{\|}{C}}-NR_{11}R_{12}$, wherein R_{11} and R_{12} are each independentlyC_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy;

C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

$-SO_2R_{13}$ wherein R_{13} is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

or $-O\overset{O}{\overset{\|}{C}}R_{14}$ wherein R_{14} is C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl; C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; Het; or C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy, hydroxy, halo, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, C_{6-10} aryl, C_{7-14} alkylaryl, C_{6-10} aryloxy, C_{7-14} alkylaryloxy, C_{8-15} alkylarylester or Het;

(d) R_4 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl, each optionally substituted from one to three times with halogen; or R_2 is H; or R_2 together with the carbon to which it is attached forms a 3, 4 or 5 membered ring;

(e) R_5 is C_{6-10} aryl; C_{7-14} alkylaryl; C_{6-10} aryloxy; C_{7-14} alkylaryloxy; C_{8-15} alkylarylester; C_{1-8} alkyl; unsubstituted C_{3-7} cycloalkyl or C_{4-10} (alkylcycloalkyl); or unsubstituted or substituted Het, said Het substituents being the same or different and being selected from one to three of halo, cyano, trifluoromethyl, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, amido, C_{1-6} alkanoylamino, amino, phenyl or phenylthio, said phenyl or phenyl portion of phenylthio being unsubstituted or substituted by one to three, same or different, substituents selected from halo, cyano, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, amido or phenyl

(f) m is 1 or 2;

(g) n is 1 or 2;

(m) R_3 is C_{1-8} alkyl optionally substituted with halo, cyano, amino, C_{1-6} dialkylamino, C_{6-10} aryl, C_{7-14} alkylaryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl, wherein the cycloalkyl or alkylcycloalkyl are optionally substituted with hydroxy, C_{1-6} alkyl, C_{2-6} alkenyl or C_{1-6} alkoxy; or R_3 together with the carbon atom to which it is attached forms a C_{3-7} cycloalkyl group optionally substituted with C_{2-6} alkenyl;

(n) Y is H, phenyl substituted with nitro, pyridyl substituted with nitro, or C_{1-6} alkyl optionally substituted with cyano, OH or C_{3-7} cycloalkyl; provided that if R_4 or R_5 is H then Yis H;

(o) B is H, C_{1-6} alkyl, R_6-(C=O)-, R_6O(C=O)-, R_6-N(R_7)-C(=O)-, R_6-N(R_7)-C(=S)-, R_6SO_2-, or R_6-N(R_7)-SO_2-;

(p) R_6 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, -OC(O)C_{1-6} alkyl, C_{1-6} alkoxy, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalklyl, each optionally substituted with hydroxy, carboxyl, (C_{1-6} alkoxy)carbonyl, amino optionally substituted with C_{1-6} alkyl, amido, or (lower alkyl) amido; (iii) C_{6-10} aryl or C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl, halogen, nitro, hydroxy, amido, (lower alkyl) amido, or amino optionally substituted with C_{1-6} alkyl; (iv) Het; (v) bicyclo(1.1.1)pentane; or (vi) -C(O)OC_{1-6} alkyl, C_{2-6}alkenyl or C_{2-6} alkynyl; and.

(q) R_7 is H; C_{1-6} alkyl optionally substituted with 1-3 halogens; or C_{1-6} alkoxy provided R_6 is C_{1-10} alkyl;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

2. The compound of claim 1, wherein R_1 is H, C_{1-6} alkyl, C_{2-4} alkenyl or phenyl.

3. The compound of claim 1, wherein R_2 is phenyl, optionally substituted with C_{1-3} alkyl, one to three chloro or one to three fluoro; or R^2 is phenyl, optionally substituted with phenyl, methoxy, phenoxy, C_{2-4} alkylester, C_{2-6} alkanoyl, nitro, thio (C_{1-4} alkyl) or carboxy.

4. The compound of claim 1, wherein R_2 is C_{1-6} alkyl or C_{3-6} cycloalkyl, all of which may be optionally substituted with a phenyl group.

5. The compound of claim 1, wherein R_2 is a six membered heterocyclic group, optionally substituted with one to three chloro or one to three fluoro, or substituted with a (C_{1-6} alkyl) carboxy.

6. The compound of claim 1, wherein R_2 is C_{2-4} alkenyl.

7. The compound of claim 1, wherein R_1 and R_2 form a five or six membered heterocyclic ring, optionally containing oxygen.

8. The compound of claim 1, wherein R_1 and R_2 form a fused ring structure comprising a five and six membered ring.

9. The compound of Claim 1 wherin R_4 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-7} cycloalkyl.

10. The compound of Claim 1 wherein R_3 is C_{1-8} alkyl optionally substituted with C_6aryl, C_{1-6} alkoxy, carboxy, hydroxy, aryloxy, C_{7-14} alkylaryloxy, C_{2-6} alkylester, C_{8-15} alkylarylester; C_{3-12} alkenyl, C_{3-7} cycloalkyl, or C_{4-10} alkylcycloalkyl.

11. The compound of Claim 10 wherein R_3 is C_{1-8} alkyl optionally substituted with C_{1-6} alkoxy; or C_{3-7} cycloalkyl.

12. The compound of Claim 11 wherein R_3 is t-butyl.

13. The compound of Claim 1 wherein Y is H.

14. The compound of Claim 1 wherein R_6 is (i) C_{1-10} alkyl optionally substituted with phenyl, carboxyl, C_{1-6} alkanoyl, 1-3 halogen, hydroxy, C_{1-6} alkoxy; (ii) C_{3-7} cycloalkyl, C_{3-7} cycloalkoxy, or C_{4-10} alkylcycloalklyl; or (iii) C_{6-10} aryl or C_{7-16} arylalkyl, each optionally substituted with C_{1-6} alkyl or halogen.

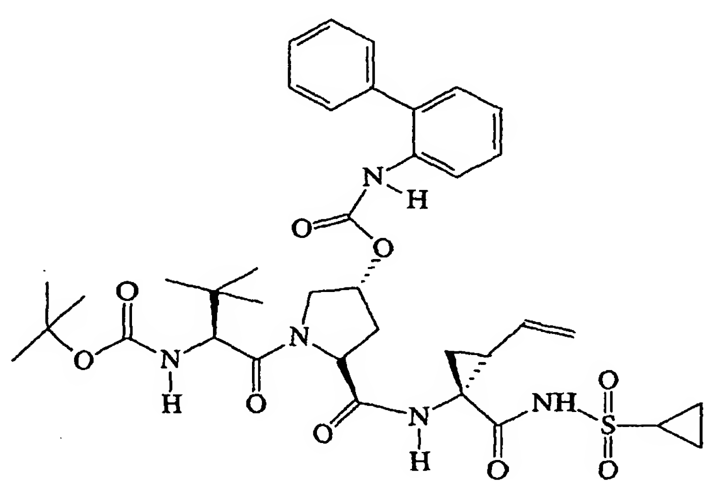
15. The compound of Claim 14 wherein R_6 is (i) C_{1-10} alkyl optionally substituted with 1-3 halogen or C_{1-6} alkoxy; or (ii) C_{3-7} cycloalkyl or C_{4-10} alkylcycloalkyl.

16. The compound of Claim 15 wherein R_6 is t-butyl.

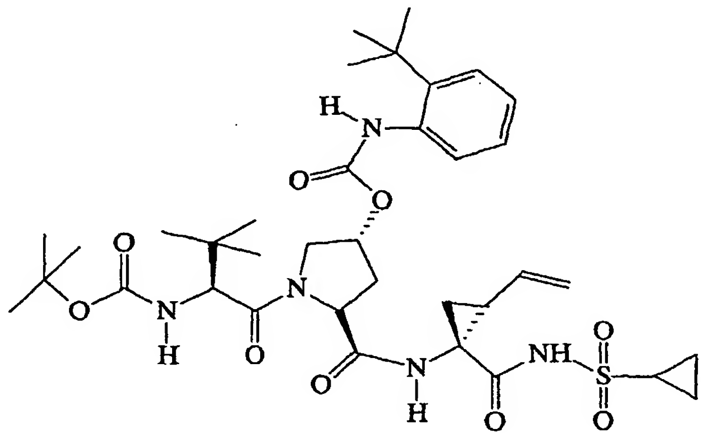
17. The compound of Claim 1 wherein R_7 is H or C_{1-6} alkyl optionally substituted with 1-3 halogens.

18. The compound of Claim 17 wherein R_7 is H.

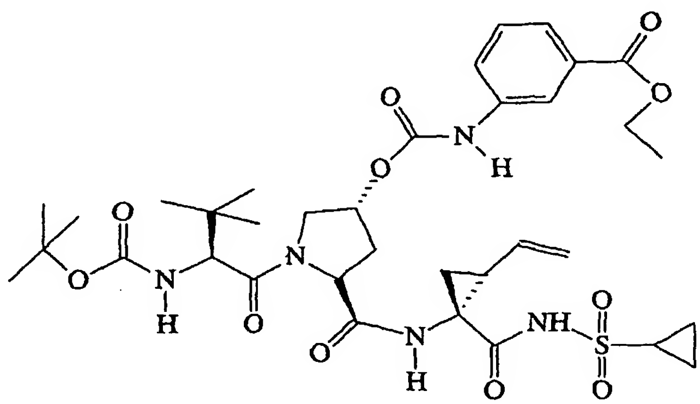
19. A compound having the formula:



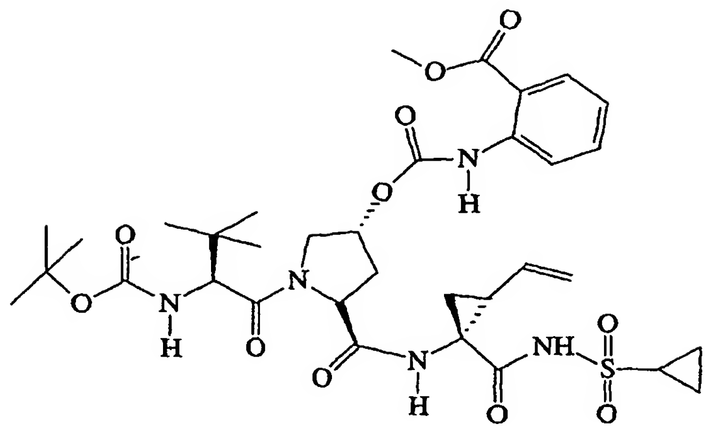
20. A compound having the formula:



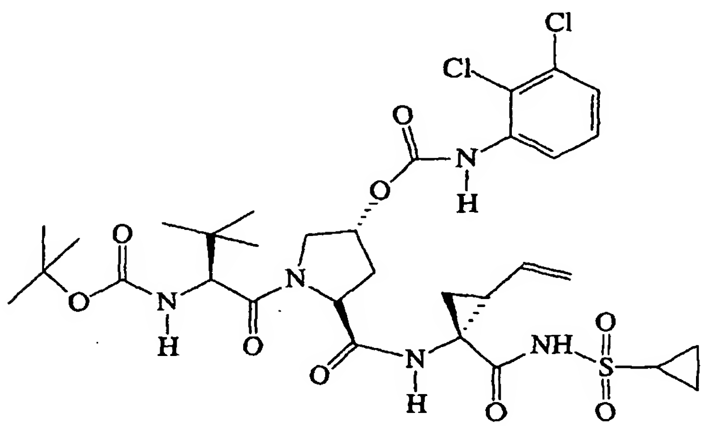
21. A compound having the formula:



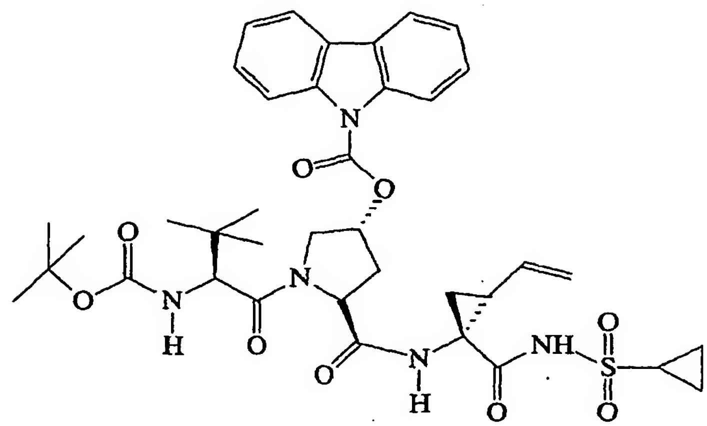
22. A compound having the formula:



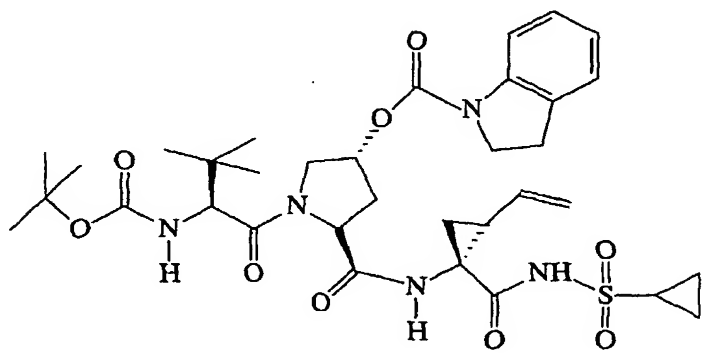
23. A compound having the formula:



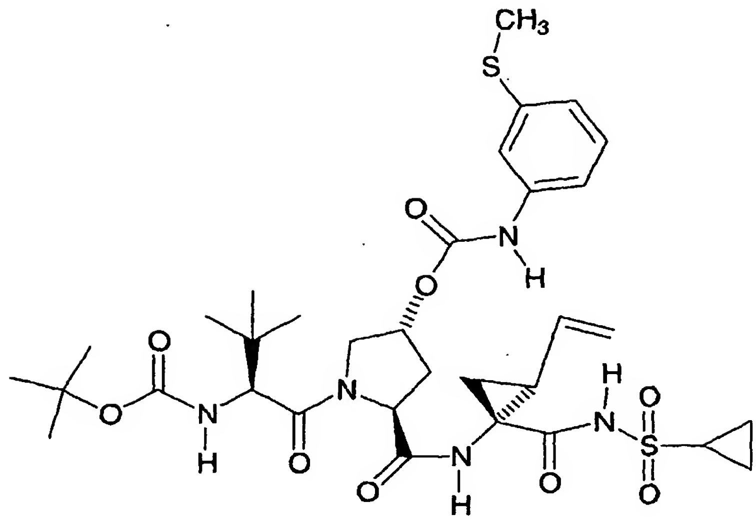
24. A compound having the formula:



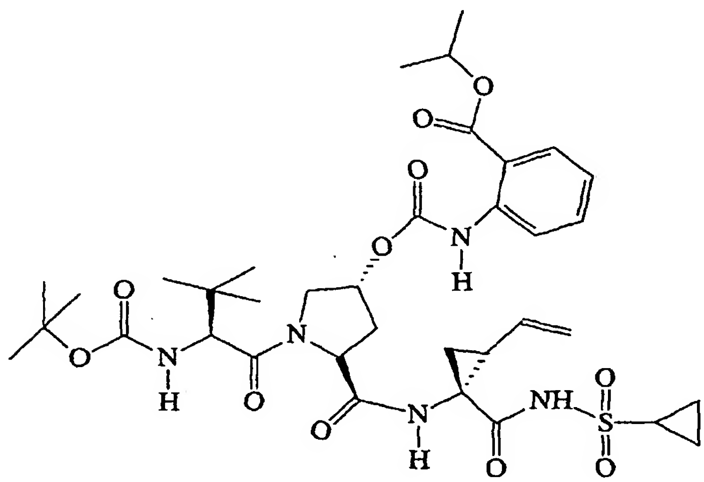
25. A compound having the formula:



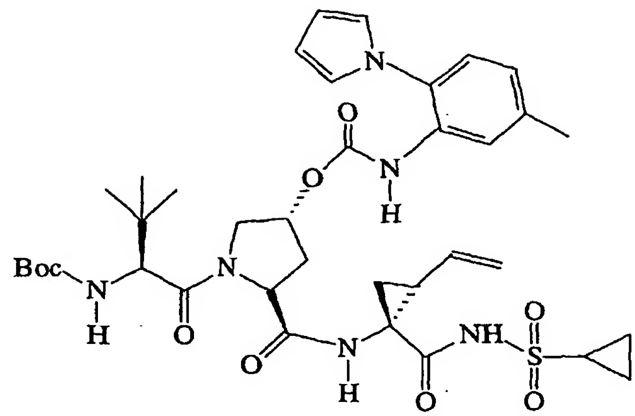
26. A compound having the formula:



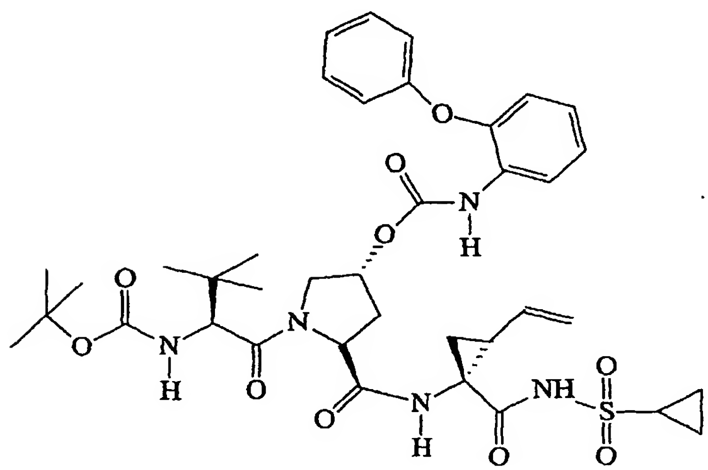
27. A compound having the formula:



28. A compound having the formula:



29. A compound having the formula:



30. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of the compound of claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof.

31. A method of inhibiting HCV NS3 protease comprising administering to a patient in need thereof a therapeutically effective amount of the compound of claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof.

32. A composition comprising the compound of claim 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof and a pharmaceutically acceptable carrier.

33. The composition of claim 32 further comprising an additional immunomodulatory agent.

34. The composition of claim 32 wherein the additional immunomodulatory agent is selected from the group consisting of α-, β-, and δ-interferons.

35. The composition of claim 32 further comprising an antiviral agent.

36. The composition of claim 35 wherein the antiviral agent is selected from the group consisting of ribavirin and amantadine.

37. The composition of claim 32 further comprising an inhibitor of HCV protease other than the compound of claim 1.

38. The composition of claim 37 further comprising an inhibitor of a target in the HCV life cycle other than HCV NS3 protease.

39. The composition of claim 38 wherein the other target is selected from the group consisting of helicase, polymerase, metalloprotease and mixtures thereof.

40. Use of the composition of claim 32 for the manufacture of a medicament for treating a hepatitis C viral infection in a patient.